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DATE: Sunday, April 11, 2004

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☐ 1. Document ID: US 20040064261 A1

L3: Entry 1 of 53 File: PGPB Apr 1, 2004

PGPUB-DOCUMENT-NUMBER: 20040064261
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040064261 A1

TITLE: Technique for analyzing arrayed signals using quantum expressor functions

PUBLICATION-DATE: April 1, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gulati, Sandeep	La Canada	CA	US	

US-CL-CURRENT: 702/19; 702/22

ABSTRACT:

A technique for determining events of interest within an output pattern generated from a detected image of an array of detectors where the output pattern comprises signals associated with noise, and signals associated with the events of interest which have intensities both greater and less than intensities of signals associated with noise. Quantum resonance interferometry is utilized to amplify signals associated with the events of interest having an intensity lower than the intensity of signals associated with noise, to an intensity greater than the intensity of the signals associated with noise to generate a modified output pattern. Once the desired signals are amplified, the technique determines which signals within the modified output pattern correlate with events of interest thus permitting a determination to be made whether a certain event of interest has occurred.

L3: Entry 1 of 53 File: PGPB Apr 1, 2004

DOCUMENT-IDENTIFIER: US 20040064261 A1
TITLE: Technique for analyzing arrayed signals using quantum expressor functions

Summary of Invention Paragraph:
[0008] Accordingly, it would highly desirable to provide an improved method and apparatus for analyzing the output of the DNA microarray to more expediently, reliably, and inexpensively determine the presence of any medical conditions or concerns within the patient providing the DNA sample. It is particularly desirable to provide a technique that can identify mutation signatures within dot spectrograms even in circumstance wherein the signal to noise ration is extremely

low. It is to these ends that aspects of the invention are generally drawn.

☐ 2. Document ID: US 20040063136 A1

L3: Entry 2 of 53 File: PGPB Apr 1, 2004

PGPUB-DOCUMENT-NUMBER: 20040063136
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040063136 A1

TITLE: Repeatable software-based active signal processing technique

PUBLICATION-DATE: April 1, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gulati, Sandeep	La Canada Flintridge	CA	US	

US-CL-CURRENT: 435/6

ABSTRACT:

A technique is disclosed that is useful for determining the presence of specific hybridization expression within an output pattern generated from a digitized image of a biological sample applied to an arrayed platform. The output pattern includes signals associated with noise, and signals associated with the biological sample, some of which are degraded or obscured by noise. The output pattern is first segmented using tessellation. Signal processing, such as interferometry, or more specifically, resonance interferometry, and even more specifically quantum resonance interferometry or stochastic resonance interferometry, is then used to amplify signals associated with the biological sample within the segmented output pattern having an intensity lower than the intensity of signals associated with noise so that they may be clearly distinguished from background noise. The improved detection technique allows repeatable, rapid, reliable, and inexpensive measurements of arrayed platform output patterns.

L3: Entry 2 of 53 File: PGPB Apr 1, 2004

DOCUMENT-IDENTIFIER: US 20040063136 A1
TITLE: Repeatable software-based active signal processing technique

Summary of Invention Paragraph:
[0010] Accordingly, it would highly desirable to provide an improved method and apparatus for analyzing the output of the DNA microarray to more expediently, reliably, and inexpensively determine the presence of any conditions within the patient providing the DNA sample. It is particularly desirable to provide a technique that can identify mutation signatures within dot spectrograms even in circumstance wherein the signal to noise ration is extremely low. It is to these ends that aspects of the invention are generally drawn.

☐ 3. Document ID: US 20040061702 A1

L3: Entry 3 of 53 File: PGPB Apr 1, 2004

PGPUB-DOCUMENT-NUMBER: 20040061702
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040061702 A1

TITLE: Methods and system for simultaneous visualization and manipulation of multiple data types

PUBLICATION-DATE: April 1, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Kincaid, Robert	Half Moon Bay	CA	US	

US-CL-CURRENT: 345/440

ABSTRACT:

Software systems, methods and recordable media for organizing and manipulating diverse data sets to facilitate identification, trends, correlations and other useful relationships among the data. Extremely large data sets such as microarray data and other biological data are graphically displayed and sorted in an effort to develop visual similarities, correlations or trends that can be seen by a user of the present invention. Various schemes for graphical representations of the data, as well as sorting schemes are provided, including sorting schemes performed relative to pseudo-data vectors.

L3: Entry 3 of 53 File: PGPB Apr 1, 2004

DOCUMENT-IDENTIFIER: US 20040061702 A1
TITLE: Methods and system for simultaneous visualization and manipulation of multiple data types

Detail Description Paragraph:

[0106] The column, row and manual sorting procedures described above can be useful in identifying correlations, trends and other relationships among the data in some instances. However, when dealing with large volumes of experimental data, such as microarray data sets or protein or other molecular data sets, the data sets are often sufficiently "noisy" that it is often difficult to find meaningful correlations by simply sorting a single column (e.g., a single array) or a single row (e.g., a single gene). When experimental data such as these are measured by very low level signals, there may be a lot variation in the measured values from experiment to experiment and they are inherently "noisy`. Microarrays are generally noisy due to a number of experimental variances. Microarrays are generally qualitatively reproducible, but the individual measurements will still show quite a bit of variance. Thus, if a sort is performed on the basis of a single or individual array, slightly different ordering results are observed, as compared to the same sort performed on an array which is already known to be similar. These differences may even occur when a sorting procedure is performed on two different

arrays representing the same experiment (i.e., a replicated experiment) due to differences in noise levels between the two arrays. To address these problems, the present invention further provides the capability of performing similarity sorting, which includes the ability to sort the data set by row or column similarity.

☐ 4. Document ID: US 20040053277 A1

L3: Entry 4 of 53 File: PGPB Mar 18, 2004

PGPUB-DOCUMENT-NUMBER: 20040053277
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040053277 A1

TITLE: Strong gene sets for glioma classification

PUBLICATION-DATE: March 18, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Zhang, Wei	Houston	TX	US	
Fuller, Greg	Houston	TX	US	
Dougherty, Ed	College Station	TX	US	
Hess, Kenneth	Houston	TX	US	

US-CL-CURRENT: 435/6; 435/7.23

ABSTRACT:

The present invention provides a number of gene markers whose expression is altered in various gliomas. In particular, by examining the expression these markers, one can accurately classify a glioma as glioblastoma multiforme (GM), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO) or oligodendroglioma (OL). The diagnosis may be performed on nucleic acids, for example, using a DNA microarray, or on protein, for example, using immunologic means. Also disclosed are methods of therapy.

L3: Entry 4 of 53 File: PGPB Mar 18, 2004

DOCUMENT-IDENTIFIER: US 20040053277 A1
TITLE: Strong gene sets for glioma classification

Detail Description Paragraph:

[0260] The inventors used a novel method to find both strong classifiers and strong features. This method is briefly described in the Materials and Methods section and is explicated in more detail in (Kim et al., 2002). This algorithm considers the inherently variable or "high-noise" nature of microarray measurements and mimics this fuzziness by adding noise to the sample sets. The basic idea is that if the data are deliberately made "worse" and classifier genes can still be identified, then these genes are very likely to be robust.

☐ 5. Document ID: US 20040038206 A1

L3: Entry 5 of 53 File: PGPB Feb 26, 2004

PGPUB-DOCUMENT-NUMBER: 20040038206
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040038206 A1

TITLE: Method for high throughput assay of genetic analysis

PUBLICATION-DATE: February 26, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Zhang, Jia	Glendora	CA	US	
Li, Kai	Glendora	CA	US	

US-CL-CURRENT: 435/6

ABSTRACT:

Methods for high throughput assay of genetic analysis are provided. Genetic materials of either DNA or RNA are used as the template for primer extension using target specific primers. Following primer extension, the extended products with labeled nucleotides integrated are kept on the solid support and used for visualization and detection. As compared to other methods for genetic assay, this method is quick, reliable, and compatible with analysis of several genetic analysis including polymorphism, gene expression profiling, and sequencing.

L3: Entry 5 of 53 File: PGPB Feb 26, 2004

DOCUMENT-IDENTIFIER: US 20040038206 A1
TITLE: Method for high throughput assay of genetic analysis

Detail Description Paragraph:

[0040] Prior to this invention, both enzymatic primer extension and oligonucleotide hybridization have been used in the analysis of polymorphism as mentioned above. These two strategies seem very different and could not been integrated in one method. Primer extension followed by gel electrophoresis is very reliable, which gives a clear answer with yes or no. But this method has several limitations. First, it is not easy to apply to multiple polymorphism sites and in high throughput assay. Second, the editing function from 3'.fwdarw.5' exonuclease activity of a variety of polymerases may cause false positive results. This false positive potential often requires a further confirmation by sequencing analysis. On the contrary, gene microarray using oligonucleotide hybridization can analyze multiple polymorphisms and is compatible with high throughput assay. However, the latter method is not as sensitive and reliable as the one using primer extension followed by gel electrophoresis. The reason for less sensitive and less reliable of the oligonucleotide hybridization is because its basic principle: identifying polymorphism by comparing the signal/noise ratio based on one base mismatch.

☐ 6. Document ID: US 20040027350 A1

L3: Entry 6 of 53 File: PGPB Feb 12, 2004

PGPUB-DOCUMENT-NUMBER: 20040027350
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040027350 A1

TITLE: Methods and system for simultaneous visualization and manipulation of multiple data types

PUBLICATION-DATE: February 12, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Kincaid, Robert	Half Moon Bay	CA	US	
Vailaya, Aditya	Santa Clara	CA	US	

US-CL-CURRENT: 345/440

ABSTRACT:

Software systems and methods for organizing and manipulating diverse data sets to facilitate identification, trends, correlations and other useful relationships among the data. Extremely large data set such as microarray data and other biological data are graphically displayed and sorted in an effort to develop visual similarities, correlations or trends that can be seen by a user of the present invention. Various schemes for graphical representations of the data, as well as sorting schemes are provided. Additionally, non-experimental or other data can be displayed and tracked along with the data upon which the sorting schemes are processed.

L3: Entry 6 of 53 File: PGPB Feb 12, 2004

DOCUMENT-IDENTIFIER: US 20040027350 A1
TITLE: Methods and system for simultaneous visualization and manipulation of multiple data types

Detail Description Paragraph:
[0102] The column, row and manual sorting procedures described above can be useful in identifying correlations, trends and other relationships among the data in some instances. However, when dealing with large volumes of experimental data, such as microarray data sets or protein or other molecular data sets, the data sets are often sufficiently "noisy" that it is often difficult to find meaningful correlations by simply sorting a single column (e.g., a single array) or a single row (e.g., a single gene). When experimental data such as these are measured by very low level signals, there may be a lot variation in the measured values from experiment to experiment and they are inherently "noisy`. Microarrays are generally noisy due to a number of experimental variances. Microarrays are generally qualitatively reproducible, but the individual measurements will still show quite a bit of variance. Thus, if a sort is performed on the basis of a single or

individual array, slightly different ordering results are observed, as compared to the same sort performed on an array which is already known to be similar. These differences may even occur when a sorting procedure is performed on two different arrays representing the same experiment (i.e., a replicated experiment) due to differences in noise levels between the two arrays. To address these problems, the present invention further provides the capability of performing similarity sorting, which includes the ability to sort the data set by row or column similarity.

☐ 7. Document ID: US 20030233197 A1

L3: Entry 7 of 53 File: PGPB Dec 18, 2003

PGPUB-DOCUMENT-NUMBER: 20030233197
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030233197 A1

TITLE: Discrete bayesian analysis of data

PUBLICATION-DATE: December 18, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Padilla, Carlos E.	Lexington	MA	US	
Karlov, Valeri I.	Framingham	MA	US	

US-CL-CURRENT: 702/20; 702/179, 702/19, 706/46, 706/52, 706/924, 707/104.1

ABSTRACT:

A probabilistic approximation of a data distribution is provided, wherein uncertain measurements in data are fused together to provide an indication of whether a new data item belongs to a given disease model. The probabilistic approximation is provided in accordance with a Bayesian analysis technique that examines the relationship of probability distributions for observable events x and multiple hypotheses H regarding those events.

L3: Entry 7 of 53 File: PGPB Dec 18, 2003

DOCUMENT-IDENTIFIER: US 20030233197 A1
TITLE: Discrete bayesian analysis of data

Detail Description Paragraph:
[0312] Gene expression signatures allowing for discrimination of breast cancer patients exhibiting a short interval (<5 years) to distant metastases from those remaining free of metastases after 5 years were identified. The data set included 78 patients: 44 patients with "good prognosis" (continued to be metastasis-free after at least 5 years) and 34 patients with "poor prognosis" (developed distant metastasis within 5 years). All patients were lymph node negative and under 55 years of age at diagnosis. Gene expression data for each patient was obtained from DNA microarrays containing 24,481 human genes and included the following fields: intensities, intensity ratios, and measurement noise characteristics (P-values).

☐ 8. Document ID: US 20030226963 A1

L3: Entry 8 of 53 File: PGPB Dec 11, 2003

PGPUB-DOCUMENT-NUMBER: 20030226963
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030226963 A1

TITLE: System and method for the preparation of arrays of biological or other molecules

PUBLICATION-DATE: December 11, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cooks, Robert G.	West Lafayette	IN	US	
Ouyang, Zheng	West Lafayette	IN	US	

US-CL-CURRENT: 250/283

ABSTRACT:

A method of separating species in a mixture of molecules, particles or atoms and collecting the separated species is described. The method comprises the steps of converting by ionization the species in the mixture to gas phase ions, separating the gas phase ions according to their mass charge ratio and/or mobility and collecting the separated ions. The system includes ionizing means such as electrospray to form the gas phase ions. The gas phase ions are separated by filtering, or in time or in space and soft-landed for collection such as on a surface.

L3: Entry 8 of 53 File: PGPB Dec 11, 2003

DOCUMENT-IDENTIFIER: US 20030226963 A1
TITLE: System and method for the preparation of arrays of biological or other molecules

Detail Description Paragraph:

[0036] In one example proteins and biomolecules were soft-landed using a linear quadrupole mass filter. A commercial Thermo Finnigan (San Jose, Calif.) SSQ 710C, FIG. 3, was modified by adding an electrospray ionization (ESI) source. The source included a syringe 31 which introduced the protein mixture into the capillary 32. A high voltage (HV) was applied between the capillary 32 and the ionization chamber (not shown) for electrospray ionization. The various chambers (not shown) and elements of the instrument and their pressures are schematically shown and identified in FIG. 3. The microarray plate 13 was mounted for x-y movement in the last evacuated chamber. An x-y microarray plate drive is not shown since its construction is well within the skill of those practicing the art. In one example a flow rate of 0.5 .mu.l/min was used throughout the experiments. The surface for ion landing was located behind the detector assembly. In the ion detection mode, the

high voltages on the conversion dynode 33 and the multiplier 34 were turned on and the ions were detected to allow the overall spectral qualities, signal-to-noise ratio and mass resolution over the full mass range to be examined. In the ion-landing mode, the voltages on the conversion dynode and the multiplier were turned off and the ions were allowed to pass through the hole in the detection assembly to reach the gold surface of the plate 13. The surface was grounded and the potential difference between the source and the surface was 0 volts.

☐ 9. Document ID: US 20030226098 A1

L3: Entry 9 of 53 File: PGPB Dec 4, 2003

PGPUB-DOCUMENT-NUMBER: 20030226098
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030226098 A1

TITLE: Methods for analysis of measurement errors in measured signals

PUBLICATION-DATE: December 4, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Weng, Lee	Bellevue	WA	US	

US-CL-CURRENT: 714/798

ABSTRACT:

The present invention provides methods for analyzing measurement errors in measured signals obtained in an experiment, e.g., measured intensity signals obtained in a microarray gene expression experiment. In particular, the invention provides a method for transforming measured signals into a domain in which the measurement errors in the transformed signals are normalized by errors as determined from an error model. The methods of the invention are particularly useful for analyzing measurement errors in signals in which at least portion of the error is dependent on the magnitudes of the signals. Such transformed signals permit analysis of data using traditional statistical methods, e.g., ANOVA and regression analysis. Magnitude-independent errors can also be used for comparing level of measurement errors in signals of different magnitudes.

L3: Entry 9 of 53 File: PGPB Dec 4, 2003

DOCUMENT-IDENTIFIER: US 20030226098 A1
TITLE: Methods for analysis of measurement errors in measured signals

Detail Description Paragraph:
[0053] Errors in measured signals can be described by error models (see, e.g., Supplementary material to Roberts et al, 2000, Science, 287:873-880; and Rocke et al., 2001, J. Computational Biology 8:557-569). In preferred embodiments, an error model (see, e.g., Supplementary material to Roberts et al, 2000, Science, 287:873-880; and Rocke et al., 2001, J. Computational Biology 8:557-569) contains two or

three error terms to describe the dominant error sources. In a two-term error model, a first error term is used to describe the low-level additive error which comes from, e.g., the background of the array chip. Since this additive error has a constant variance, in this disclosure, it is also called the constant error. The constant error is independent from the hybridization levels of individual spots on a microarray. It may come from the combination of the scanner electronics noise and/or fluorescence due to nonspecific binding of fluorescence molecules to the surface of the microarray. In one embodiment, this constant additive error is taken to have a normal distribution with a mean bkg and a standard deviation .sigma..sub.bkg. After background level subtraction, which is typically applied in microarray data processing, the additive mean bkg becomes zero. In this disclosure, it is often assumed that the background intensity offset has been corrected. An ordinary skilled artisan in the art will appreciate that in cases where the background mean is not corrected, the methods of the invention can be used with an additional step of making such a correction.

☐ 10. Document ID: US 20030224385 A1

L3: Entry 10 of 53 File: PGPB Dec 4, 2003

PGPUB-DOCUMENT-NUMBER: 20030224385
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030224385 A1

TITLE: Targeted genetic risk-stratification using microarrays

PUBLICATION-DATE: December 4, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Pihan, German	Weston	MA	US	

US-CL-CURRENT: 435/6; 435/91.2

ABSTRACT:

The invention relates to new expedient and cost-effective assays that are capable of identifying many or all relevant diagnostic and prognostic genetic lesions in cancer or cancer predisposition using multiplex PCR or other nucleic acid amplification or enrichment technology in conjunction with bead microarrays for the purpose of risk-stratifying patients with cancer or cancer predisposition. The new assay methods are referred to herein as BARCODE-MT for Bead ARray COded DEtection of Multiple Targets. These assays are high-throughput, and can be automated for highly accurate diagnoses that can be used to optimize risk-adapted therapy.

L3: Entry 10 of 53 File: PGPB Dec 4, 2003

DOCUMENT-IDENTIFIER: US 20030224385 A1
TITLE: Targeted genetic risk-stratification using microarrays

Detail Description Paragraph:

[0031] The new BARCODE-MT assay provides fast and accurate analysis of clinical samples by multiplexing target testing at both the amplification and detection steps. For multiplex detection, the invention uses bead microarrays because of their attractive cost/sample ratio and the flexibility of the format for devising new tests or modifying existing ones. The use of bead microarrays solves the conundrum of multiplex PCR, i.e., the increasing difficulty in unambiguously identifying a specifically amplified target by size alone (e.g., by gel electrophoresis or capillary electrophoresis) as the number of possible targets increases. Because bead microarrays are customized and compatible with fast flow read-through systems, fluid phase bead microarrays compare favorably with solid phase arrays for these types of assays. The adoption of a high-speed hybridization-based detection method is also amenable to automation, which is an important feature, because automation reduces operator input and the associated risk of error. Because of the favorable signal-to-noise ratio of our assay, case calling is unambiguous as demonstrated by the mixing and coding experiments described below, as well as the perfect correlation between single target PCR and BARCODE-MT.

☐ 11. Document ID: US 20030219797 A1

L3: Entry 11 of 53 File: PGPB Nov 27, 2003

PGPUB-DOCUMENT-NUMBER: 20030219797
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030219797 A1

TITLE: Statistical modeling to analyze large data arrays

PUBLICATION-DATE: November 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Zhao, Lue Ping	Bellevue	WA	US	
Prentice, Ross	Seattle	WA	US	
Breeden, Linda	Seattle	WA	US	

US-CL-CURRENT: 435/6; 702/20

ABSTRACT:

A method for analyzing large data arrays is provided. In one aspect, the invention provides a method for analyzing data from two or more data arrays. Each array includes a plurality of members, each member provides a signal, and the data is indexed by one or more parameters. In one embodiment, the method includes fitting a model to the data; determining the goodness of the fit by evaluating the statistical significance of the fit; and determining the statistical significance of the signal. In another embodiment, the method further includes correcting the data for heterogeneity among members prior to fitting the model to the data.

L3: Entry 11 of 53 File: PGPB Nov 27, 2003

DOCUMENT-IDENTIFIER: US 20030219797 A1

TITLE: Statistical modeling to analyze large data arrays

Detail Description Paragraph:
[0070] Accordingly, one embodiment of the invention employs a statistical model (SPM) to identify and characterize single pulses of transcription that occur at invariant times in consecutive cell cycles. SPM is a specific application of statistical modeling, but the basic strategy can be applied to any large data set to identify genes undergoing a transcriptional response to a stimulus. Due to its relative simplicity, statistical modeling can be used to interrogate large data sets without employing additional filters to reduce the number of genes to be analyzed. It also includes heterogeneity parameters that will tend to reduce the impact of noise in the data sets. SPM identifies regularly oscillating transcripts without regard to the abundance of the transcript or the height or timing of the peak, and provides estimates of the mean time of activation and deactivation. These values are only estimates, but they are unbiased under the assumed SPM and can be considered defining characteristics of individual genes. SPM also provides statistical measures of the quality of the parameter estimates so that optimal groupings can be made and subjected to further analysis. These features of statistical modeling complement and augment the other methods used to analyze microarray data.

☐ 12. Document ID: US 20030219764 A1

L3: Entry 12 of 53 File: PGPB Nov 27, 2003

PGPUB-DOCUMENT-NUMBER: 20030219764
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030219764 A1

TITLE: Biological discovery using gene regulatory networks generated from multiple-disruption expression libraries

PUBLICATION-DATE: November 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Imoto, Seiya	Tokyo		JP	
Goto, Takao	Tokyo		JP	
Miyano, Satoru	Tokyo		JP	
Tashiro, Kosuke	Higashi-ku		JP	
de Hoon, Michiel J.L	Tokyo		JP	
Savoie, Christopher J.	Yanagawa		JP	
Kuhara, Saturo	Minami-Ku		JP	

US-CL-CURRENT: 435/6; 702/20

ABSTRACT:

Embodiments of this invention include application of new inferential methods to analysis of complex biological information, including gene networks. In some

embodiments, disruptant data and/or drug induction/inhibition data are obtained simultaneously for a number of genes in an organism. New methods include modifications of Boolean inferential methods and application of those methods to determining relationships between expressed genes in organisms. Additional new methods include modifications of Bayesian inferential methods and application of those methods to determining cause and effect relationships between expressed genes, and in some embodiments, for determining upstream effectors of regulated genes. Additional modifications of Bayesian methods include use of heterogeneous variance and different curve fitting methods, including spline functions, to improve estimation of graphs of networks of expressed genes. Other embodiments include the use of bootstrapping methods and determination of edge effects to more accurately provide network information between expressed genes. Methods of this invention were validated using information obtained from prior studies, as well as from newly carried out studies of gene expression.

L3: Entry 12 of 53 File: PGPB Nov 27, 2003

DOCUMENT-IDENTIFIER: US 20030219764 A1
TITLE: Biological discovery using gene regulatory networks generated from multiple-disruption expression libraries

Detail Description Paragraph:
[0178] In cDNA microarray experiments, gene expression levels are typically measured at a small number of time points. Conventional techniques of time series analysis, such as Fourier analysis or autoregressive or moving-average modeling, are not suitable for such a small number of data points. Instead, the gene expression data are often analyzed by clustering techniques or by considering the relative change in the gene expression level only. Such a "fold-change" analysis may miss significant changes in gene expression levels, while it may inadvertently attribute significance to measurements dominated by noise. In addition, a fold-change analysis may not be able to identify important features in the temporal gene expression response.

☐ 13. Document ID: US 20030219760 A1

L3: Entry 13 of 53 File: PGPB Nov 27, 2003

PGPUB-DOCUMENT-NUMBER: 20030219760
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030219760 A1

TITLE: Diagnostic and prognostic tests

PUBLICATION-DATE: November 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gordon, Gavin J.	Brighton	MA	US	
Jensen, Roderick V.	Pelham	CT	US	
Gullans, Steven R.	Natick	MA	US	
Bueno, Raphael	Brookline	MA	US	

US-CL-CURRENT: 435/6; 702/20

ABSTRACT:

The invention provides methods for diagnosing biological states or conditions based on ratios of gene expression data from tissue samples, such as cancer tissue samples. The invention also provides sets of genes that are expressed differentially in malignant pleural mesothelioma. These sets of genes can be used to discriminate between normal and malignant tissues, and between classes of malignant tissues. Accordingly, diagnostic assays for classification of tumors, prediction of tumor outcome, selecting and monitoring treatment regimens and monitoring tumor progression/regression also are provided.

L3: Entry 13 of 53 File: PGPB Nov 27, 2003

DOCUMENT-IDENTIFIER: US 20030219760 A1
TITLE: Diagnostic and prognostic tests

Detail Description Paragraph:
[0247] Identification of prognostic molecular markers in mesothelioma. We have previously identified for study a representative cohort of 31 mesothelioma tumors obtained at pneumonectomy (17). The estimated median patient survival (11 months, FIG. 6A) and histological distribution of this group mirror those of mesothelioma patients in our practice (6). The histological subtype of the tumor was not predictive of outcome for these samples (P=0.129, log-rank test, FIG. 6B), even though the estimated median survival of epithelial subtypes samples (17 months) was longer than that for non-epithelial subtype samples (8.5 months). To identify genes that are discriminatory between tumors from patients with widely divergent survival and to create an expression ratio-based predictor model, we utilized microarray data (17) for mesothelioma samples that originated from patients whose survival was within the 25.sup.th percentile of both disease-related survival extremes irrespective of tumor histological subtype (i.e., the training set, n=17, Table 9A). We formed two groups using these samples: relatively good outcome (survival .gtoreq.17 months, n=8) and relatively poor outcome (survival .ltoreq.6 months, n=9). The most accurate model developed in the training set was subsequently tested in an independent cohort of samples (i.e. the test set, n=29, Table 9B). We searched all of the genes represented on the microarray for those with a statistically significant .gtoreq.2-fold difference in average expression levels between good outcome and poor outcome tumors in the training set of samples. To minimize the effects of background noise, the list of distinguishing genes was further refined by requiring that the mean expression level be >500 in at least one of the two sample sets. We identified a total of 46 prognostic genes in this analysis with an estimated false discovery rate of 10%-20%. The 10 genes with the lowest P values overexpressed in each group are listed in Table 10.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 14. Document ID: US 20030219150 A1

L3: Entry 14 of 53 File: PGPB Nov 27, 2003

PGPUB-DOCUMENT-NUMBER: 20030219150
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030219150 A1

TITLE: Method, system, and computer code for finding spots defined in biological microarrays

PUBLICATION-DATE: November 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Niles, Richard K.	San Francisco	CA	US	
Martens, Christine L.	Portola Valley	CA	US	
Foskett, Darach B.	San Francisco	CA	US	

US-CL-CURRENT: 382/128

ABSTRACT:

A method (and system) for using information contained within the scanned image to create, in an automated (or semi-automated) process, an accurate data grid. The process has steps: enhance the image; locate blocks of spots; and find each individual spot in each of the blocks. Preferably, the method makes use of image filtering using a "Principal Frequency Filter" based on a mathematical determination of major periodic elements in the image to eliminate noisy, non-periodic signals, and of smoothed intensity profiles of the filtered image data. Here, the term Principal Frequency Filter is used to indicate an image-enhancing filter based upon a mathematical operation which identifies the major periodic components of the image.

L3: Entry 14 of 53 File: PGPB Nov 27, 2003

DOCUMENT-IDENTIFIER: US 20030219150 A1
TITLE: Method, system, and computer code for finding spots defined in biological microarrays

Summary of Invention Paragraph:
[0013] In an alternative specific embodiment, the invention provides a method for processing data in digital images of biological microarrays to identify one or more groupings of spots present in the microarray image. The method receives a captured image of a biological microarray of spots in an electronic format. The array itself, which is the source of the image, in most cases is composed of a plurality of groupings of spots. The groupings may be defined by 1 through N, where N is an integer greater than 1, and each of the groupings is separated by an isolation region, which is substantially free from any spots. The method processes the captured electronic image to reduce background noise. A step of identifying at least the isolation region between the groupings in the captured image using a filter applied to the captured image is included. The filter is described according to periodic components of the captured image, where the periodic components are defined by a spatial distribution of the spots in the array image. The method determines the boundaries of each grouping in the digital image of the biological microarray to isolate any one of the groupings from any one of the other groupings, and stores the locations of each grouping in the image of the biological microarray into memory.

Summary of Invention Paragraph:
[0018] In a specific embodiment, many array manufacturing methods print DNA spots in groups of approximately uniform size, e.g., blocks of 25 columns and 28 rows, though any numbers can be chosen. In some cases there may be variation in the size of blocks found on an array. Localization of spots is simplified and improved by

analyzing separately each block or grouping of spots on the image of the microarray. Thus the invention first uses a procedure to locate, on the image of the microarray, the limits of each block by identifying the spaces between blocks, in which the only signals present are background noise. These spaces can be detected as troughs in a smoothed, filtered one-dimensional intensity profile which is obtained by averaging the intensity of fluorescence emission along rows or columns in the image of the microarray. However, factors often can cause a significant reduction of the depth of such intensity profile troughs: primarily, deviation of the rows or columns from the perfect perpendicular, and background noise. The invention uses processes to avoid these problems. To minimize or reduce the damping effects of rotation on the intensity profile, rows of blocks along the shorter dimension of the image are located first. Then each row of blocks is analyzed to locate individual blocks within that row.

Summary of Invention Paragraph:
[0019] Further, to reduce the effect of background fluorescence ("noise"), the invention uses the Principal Frequency Filter, or PFF, as will be referenced herein. Briefly, this filter is defined from the digital image of the microarray by calculating a one-dimensional Fourier transformation and deriving from it the power spectrum of each row of pixels. Preferably, spectra are averaged across all rows of pixels in the image, and all peaks that occur in a small neighborhood of defined width are located. The first local peak away from zero frequency is the Principal Frequency, which is the spatial frequency determined by the repeating spot pattern. Random, non-periodic background or noise is spread out in the Fourier domain; periodic signals are concentrated into the Principal Frequency, with little contamination of this frequency by noisy nonperiodic signals. Utilizing Fourier transformation thus separates the pattern of important signals from spurious background signals. An intensity profile is determined from the power spectra of individual rows of pixels in a small neighborhood of the Principal Frequency, which eliminates the contributions of non-periodic background. The Principal Frequency intensity profile is then smoothed by a value of 1.5 times the estimated row spacing to reduce further the impact of noise and interspot spacing on the profile. Thresholding of the filtered intensity profile identifies locations of block edges along the long dimension of the array.

Detail Description Paragraph:
[0038] The block-finding process is based on the premise that the gaps in fluorescence intensity which occur between blocks can be located by identifying troughs in a smoothed one-dimensional intensity profile obtained by averaging the intensity of fluorescence emission along rows or columns. However, both rotation and background noise, common characteristics of printed microarrays which are likely to be encountered on nearly every array, can significantly reduce the depth of the intensity profile troughs, so the invention uses two different methods to correct for these potential problems. To minimize the deleterious effect of rotation, rows of blocks along the shorter dimension of the image are found first, and then each row is analyzed to locate individual blocks within the row. To minimize the effect of noise, this invention uses an image enhancing filter known as the "Principal Frequency Filter" (PFF). This filter is defined in the following manner. The one-dimensional power spectrum is calculated for each row of pixels: the number of pixels in each row is increased to a power of 2 to allow a fast Fourier transformation (FFT) to be used. The FFT is calculated; and the power spectrum is computed by summing the squares of the real and imaginary components of the FFT. Next, the Principal Frequency is identified: the one-dimensional row power spectra are averaged across all rows of pixels in the image to compute the average row power spectrum; all peaks are located which occur in the average row power spectrum in neighborhoods of an optimal width, for example 2.5%, of the adjusted row dimension. The first non-zero local peak is the Principal Frequency, which is the spatial frequency determined by the repeating spot pattern. "Peaks" are defined either as local maxima within the defined neighborhood for a positive image, in which spots appear as bright areas on a dark background, or as local minima within

the defined neighborhood for a negative image, in which spots appear as dark areas on a bright background. For simplicity, we refer to peaks as high values or local maxima in a positive image, but the alternative definition is also intended.

CLAIMS:

4. A method for processing data in digitized images of biological microarrays to identify one or more groupings of spots present in the microarray, the method comprising: importing a captured digitized image of a biological microarray of spots in an electronic format, the array comprising a plurality of approximately rectangular groupings of spots, called blocks, the groupings being defined by 1 through N, where N is an integer greater than 1, the blocks being arranged in a regular pattern, with rows and columns of blocks being separated by substantially horizontal and vertical isolation regions comprising background, the background regions being long, narrow areas approximating a rectangular shape, which are substantially free from any spots; processing the captured image to reduce background noise from the captured image; identifying at least the isolation region between the groupings in the captured image using a frequency domain filter applied to the captured image, the filter being constructed according to periodic components of the captured image, the periodic components being defined by a spatial distribution of the spots in the captured image of the microarray; determining the locations of the boundaries of the groupings in the captured image of the biological microarray to isolate any one of the groupings from any one of the other groupings; and storing the locations of the boundaries of the groupings in the captured image of the biological microarray into memory.

☐ 15. Document ID: US 20030194734 A1

L3: Entry 15 of 53 File: PGPB Oct 16, 2003

PGPUB-DOCUMENT-NUMBER: 20030194734
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030194734 A1

TITLE: Selection of markers

PUBLICATION-DATE: October 16, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Jatkoe, Tim	La Jolla	CA	US	

US-CL-CURRENT: 435/6; 702/20

ABSTRACT:

Methods of selecting a portfolio of markers for use in a diagnostic applications include defining diagnostic parameters, establishing a relationship among the parameters so that they are optimized, and selecting an optimal group of markers for the diagnostic application. The diagnostic parameters can include a measure of

the relative degree of expression of a gene, a measure of the variation in the measurement of the degree of expression of the gene, and the relationship between the diagnostic and discriminating parameters can be a mean variance relationship.

Machines programmed to conduct the method and articles that comprise instructions for their operation are further aspects of the invention.

L3: Entry 15 of 53 File: PGPB Oct 16, 2003

DOCUMENT-IDENTIFIER: US 20030194734 A1
TITLE: Selection of markers

Summary of Invention Paragraph:
[0014] Genes can be grouped so that information obtained about the set of genes in the group provides a sound basis for making clinically relevant judgments such as a diagnosis, prognosis, or treatment choice. These sets of genes make up the portfolios of the invention. As with most diagnostic markers, it is often desirable to use the fewest number of markers sufficient to make a correct medical judgment. This prevents a delay in treatment pending further analysis as well as inappropriate use of time and resources. Preferred optimal portfolio is one that employs the fewest number of markers for making such judgments while meeting conditions that maximize the probability that such judgments are indeed correct. These conditions will generally include sensitivity and specificity requirements. In the context of microarray based detection methods, the sensitivity of the portfolio can be reflected in the fold differences exhibited by a gene's expression in the diseased or aberrant state relative to the normal state. The detection of the differential expression of a gene is sensitive if it exhibits a large fold change relative to the expression of the gene in another state. Another aspect of sensitivity is the ability to distinguish signal from noise. For example, while the expression of a set of genes may show adequate sensitivity for defining a given disease state, if the signal that is generated by one (e.g., intensity measurements in microarrays) is below a level that easily distinguished from noise in a given setting (e.g., a clinical laboratory) then that gene should be excluded from the optimal portfolio. A procedure for setting conditions such as these that define the optimal portfolio can be incorporated into the inventive methods.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 16. Document ID: US 20030194733 A1

L3: Entry 16 of 53 File: PGPB Oct 16, 2003

PGPUB-DOCUMENT-NUMBER: 20030194733
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030194733 A1

TITLE: Cancer diagnostic panel

PUBLICATION-DATE: October 16, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wang, Yixin	San Diego	CA	US	

US-CL-CURRENT: 435/6; 536/24.3

ABSTRACT:

A method of diagnosing cancer by identifying differential modulation of each gene (relative to the expression of the same genes in a normal population) in a combination of genes selected from two groups of genes.

Gene expression portfolios and kits for employing the method are further aspects of the invention.

L3: Entry 16 of 53 File: PGPB Oct 16, 2003

DOCUMENT-IDENTIFIER: US 20030194733 A1
TITLE: Cancer diagnostic panel

Summary of Invention Paragraph:
[0013] Genes can be grouped so that information obtained about the set of genes in the group provides a sound basis for making clinically relevant judgments such as a diagnosis, prognosis, or treatment choice. These sets of genes make up the portfolios of the invention. As with most diagnostic markers, it is often desirable to use the fewest number of markers sufficient to make a correct medical judgment. This prevents a delay in treatment pending further analysis as well as inappropriate use of time and resources. Preferred optimal portfolio is one that employs the fewest number of markers for making such judgments while meeting conditions that maximize the probability that such judgments are indeed correct. These conditions will generally include sensitivity and specificity requirements. In the context of microarray based detection methods, the sensitivity of the portfolio can be reflected in the fold differences exhibited by a gene's expression in the diseased or aberrant state relative to the normal state. The detection of the differential expression of a gene is sensitive if it exhibits a large fold change relative to the expression of the gene in another state. Another aspect of sensitivity is the ability to distinguish signal from noise. For example, while the expression of a set of genes may show adequate sensitivity for defining a given disease state, if the signal that is generated by one (e.g., intensity measurements in microarrays) is below a level that easily distinguished from noise in a given setting (e.g., a clinical laboratory) then that gene should be excluded from the optimal portfolio. A procedure for setting conditions such as these that define the optimal portfolio can be incorporated into the inventive methods.

☐ 17. Document ID: US 20030194711 A1

L3: Entry 17 of 53 File: PGPB Oct 16, 2003

PGPUB-DOCUMENT-NUMBER: 20030194711
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030194711 A1

TITLE: System and method for analyzing gene expression data

PUBLICATION-DATE: October 16, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Zapala, Matthew	La Jolla	CA	US	
Lockhart, David	Del Mar	CA	US	
Barlow, Carrolee	Del Mar	CA	US	
Greenhall, Jennifer A.	San Diego	CA	US	

US-CL-CURRENT: 435/6; 702/20

ABSTRACT:

A system and methods for identifying sequence diversity in a gene or expressed sequence is disclosed wherein hybridization differences arising from polymorphic bases in analogous expressed sequences are identified between two or more nucleotide populations. By scaling the hybridization data to account for differences in abundance and observed intensity, sequence diversity can be identified in a highly specific and sensitive manner. Data confidence levels are also accounted for to increase the accuracy of the sequence diversity determination. The invention can be applied to both newly collected gene expression data and archived data to generate valuable insight into polymorphic behavior within complex nucleotide populations.

L3: Entry 17 of 53 File: PGPB Oct 16, 2003

DOCUMENT-IDENTIFIER: US 20030194711 A1
TITLE: System and method for analyzing gene expression data

Detail Description Paragraph:
[0062] In one embodiment, during or subsequent to the abovementioned differencing or scaling procedures, an outlier removal function may be used to identify and remove data that exceeds a statistical threshold of reliability. Outlier data is characterized by spurious or inaccurate hybridization/intensity values and may not reflect actual hybridization intensities expected for a particular sequence. Outlier data may arise from experimental error or inaccuracy, systematic errors, localized regions of abnormally high and/or low intensity on the surface of the microarray, and other sources. The analytical methods for sequence diversity determination may desirably incorporate methods to identify outlier data for example by identifying data which exceeds a statistical threshold of reliability. Furthermore, inadequate hybridization signals from samples where a gene is not present are filtered out before analysis to prevent identifying differences due only to a background signal of noise and not to real sequence differences. These data may then be excluded from further analysis to minimize improperly identified sequence differences (e.g., false positives). Additional details of the methods used for determining statistical reliability of the data will be described in greater detail hereinbelow.

☐ 18. Document ID: US 20030190656 A1

L3: Entry 18 of 53 File: PGPB Oct 9, 2003

PGPUB-DOCUMENT-NUMBER: 20030190656

PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030190656 A1

TITLE: Breast cancer prognostic portfolio

PUBLICATION-DATE: October 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wang, Yixin	San Diego	CA	US	

US-CL-CURRENT: 435/6

ABSTRACT:

A method of prognosticating metastasis in a breast cancer patient involves identifying differential modulation of each gene (relative to the expression of the same genes in a normal population) in a combination of genes selected from a group consisting of genes.

Gene expression portfolios and kits for employing the method are further aspects of the invention.

L3: Entry 18 of 53 File: PGPB Oct 9, 2003

DOCUMENT-IDENTIFIER: US 20030190656 A1
TITLE: Breast cancer prognostic portfolio

Summary of Invention Paragraph:
[0013] Genes can be grouped so that information obtained about the set of genes in the group provides a sound basis for making clinically relevant judgments such as a diagnosis, prognosis, or treatment choice. These sets of genes make up the portfolios of the invention. As with most diagnostic markers, it is often desirable to use the fewest number of markers sufficient to make a correct medical judgment. This prevents a delay in treatment pending further analysis as well as inappropriate use of time and resources. Preferred optimal portfolio is one that employs the fewest number of markers for making such judgments while meeting conditions that maximize the probability that such judgments are indeed correct. These conditions will generally include sensitivity and specificity requirements. In the context of microarray based detection methods, the sensitivity of the portfolio can be reflected in the fold differences exhibited by a gene's expression in the diseased or aberrant state relative to the normal state. The detection of the differential expression of a gene is sensitive if it exhibits a large fold change relative to the expression of the gene in another state. Another aspect of sensitivity is the ability to distinguish signal from noise. For example, while the expression of a set of genes may show adequate sensitivity for defining a given disease state, if the signal that is generated by one (e.g., intensity measurements in microarrays) is below a level that easily distinguished from noise in a given setting (e.g., a clinical laboratory) then that gene should be excluded from the optimal portfolio. A procedure for setting conditions such as these that define the optimal portfolio can be incorporated into the inventive methods.

☐ 19. Document ID: US 20030186303 A1

L3: Entry 19 of 53 File: PGPB Oct 2, 2003

PGPUB-DOCUMENT-NUMBER: 20030186303
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030186303 A1

TITLE: Colorectal cancer diagnostics

PUBLICATION-DATE: October 2, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wang, Yixin	San Diego	CA	US	

US-CL-CURRENT: 435/6; 536/24.3

ABSTRACT:

A method of assessing the presence or absence of colorectal cancer or the likely condition of a person believed to have colorectal cancer is conducted by analyzing the expression of a group of genes. Gene expresson profiles in a variety of medium such as microarrays are included as are kits that contain them.

L3: Entry 19 of 53 File: PGPB Oct 2, 2003

DOCUMENT-IDENTIFIER: US 20030186303 A1
TITLE: Colorectal cancer diagnostics

Summary of Invention Paragraph:
[0016] Statistical values can be used to confidently distinguish modulated from non-modulated genes and noise. Statistical tests find the genes most significantly different between diverse groups of samples. The Student's t-test is an example of a robust statistical test that can be used to find significant differences between two groups. The lower the p-value, the more compelling the evidence that the gene is showing a difference between the different groups. Nevertheless, since microarrays measure more than one gene at a time, tens of thousands of statistical tests may be asked at one time. Because of this, there is likelihood to see small p-values just by chance and adjustments for this using a Sidak correction as well as a randomization/permutation experiment can be made. A p-value less than 0.05 by the t-test is evidence that the gene is significantly different. More compelling evidence is a p-value less then 0.05 after the Sidak correct is factored in. For a large number of samples in each group, a p-value less than 0.05 after the randomization/permutation test is the most compelling evidence of a significant difference.

☐ 20. Document ID: US 20030186302 A1

L3: Entry 20 of 53 File: PGPB Oct 2, 2003

PGPUB-DOCUMENT-NUMBER: 20030186302
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030186302 A1

TITLE: Colorectal cancer diagnostics

PUBLICATION-DATE: October 2, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wang, Yixin	San Diego	CA	US	

US-CL-CURRENT: 435/6; 435/287.2

ABSTRACT:

A method of assessing the presence or absence of colorectal cancer or the likely condition of a person believed to have colorectal cancer is conducted by analyzing the expression of a group of genes. Gene expresson profiles in a variety of medium such as microarrays are included as are kits that contain them.

L3: Entry 20 of 53 File: PGPB Oct 2, 2003

DOCUMENT-IDENTIFIER: US 20030186302 A1
TITLE: Colorectal cancer diagnostics

Summary of Invention Paragraph:
[0016] Statistical values can be used to confidently distinguish modulated from non-modulated genes and noise. Statistical tests find the genes most significantly different between diverse groups of samples. The Student's t-test is an example of a robust statistical test that can be used to find significant differences between two groups. The lower the p-value, the more compelling the evidence that the gene is showing a difference between the different groups. Nevertheless, since microarrays measure more than one gene at a time, tens of thousands of statistical tests may be asked at one time. Because of this, there is likelihood to see small p-values just by chance and adjustments for this using a Sidak correction as well as a randomization/permutation experiment can be made. A p-value less than 0.05 by the t-test is evidence that the gene is significantly different. More compelling evidence is a p-value less then 0.05 after the Sidak correct is factored in. For a large number of samples in each group, a p-value less than 0.05 after the randomization/permutation test is the most compelling evidence of a significant difference.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 21. Document ID: US 20030143591 A1

L3: Entry 21 of 53 File: PGPB Jul 31, 2003

PGPUB-DOCUMENT-NUMBER: 20030143591
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030143591 A1

TITLE: Nucleic acid probes and methods to detect and/or quantify nucleic acid analytes

PUBLICATION-DATE: July 31, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Davies, Martin	Kent		GB	
Bruce, Ian	East Sussex		GB	
Wolter, Andreas	Hamburg		DE	

US-CL-CURRENT: 435/6; 536/24.3

ABSTRACT:

The invention comprises novel methods and strategies to detect and/or quantify nucleic acid analytes. The methods involve nucleic acid probes with covalently conjugated dyes, which are attached either at adjacent nucleotides or at the same nucleotide of the probe and novel linker molecules to attach the dyes to the probes. The nucleic acid probes generate a fluorescent signal upon hybridization to complementary nucleic acids based on the interaction of one of the attached dyes, which is either an intercalator or a DNA groove binder, with the formed double stranded DNA. The methods can be applied to a variety of applications including homogeneous assays, real-time PCR monitoring, transcription assays, expression analysis on nucleic acid microarrays and other microarray applications such as genotyping (SNP analysis). The methods further include pH-sensitive nucleic acid probes that provide switchable fluorescence signals that are triggered by a change in the pH of the medium.

L3: Entry 21 of 53 File: PGPB Jul 31, 2003

DOCUMENT-IDENTIFIER: US 20030143591 A1
TITLE: Nucleic acid probes and methods to detect and/or quantify nucleic acid analytes

Detail Description Paragraph:
[0207] In a conventional assay that is based on microarrays with fluorescent methods, the array needs to be stringently washed in order to remove non-hybridized fluorescent nucleotide sequences that interfere with the detection of the fluorescent signal and increase the signal to noise ratio in the assay. In these assays a delicate balance must be achieved with respect to the stringency of the washing. A stringency that is too high removes correctly hybridized sequences, which decreases positive signals in the assay, and a stringency that is too low increases false positive signals leading to unreliable and erroneous results. Often, unspecific absorption of fluorescent nucleic acids on the surface of microarrays is a major problem in these assays as the background fluorescence generated from such absorption processes can't be removed effectively. This is particularly true for surfaces modified with chemical agents that provide aminated surfaces. An aminated surface provides a positively charged matrix that attracts all negatively charged nucleic acid species in a sample in a non-specific manner.

Detail Description Paragraph:
[0208] The nucleic acid probes described herein require less stringent washes because the probes generate positive signals if and only if they are correctly hybridized on the array. Under optimized conditions the nucleic acid probes can be applied even without washes, because the probes themselves are non-fluorescent and

do not produce a background. This feature greatly diminishes the cost of microarray based assays, increases the signal to noise ratio of the assay and therefore its reliability and allows the analysis of smaller and/or more dilute nucleic acid target samples.

☐ 22. Document ID: US 20030139886 A1

L3: Entry 22 of 53 File: PGPB Jul 24, 2003

PGPUB-DOCUMENT-NUMBER: 20030139886
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030139886 A1

TITLE: Method and apparatus for normalization and deconvolution of assay data

PUBLICATION-DATE: July 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Bodzin, Leon J.	San Diego	CA	US	
Yguerabide, Juan	La Jolla	CA	US	
Warden, Laurence	Poway	CA	US	
Anderson, Richard R.	Encinitas	CA	US	
Rhodes, Kate	Poway	CA	US	

US-CL-CURRENT: 702/28

ABSTRACT:

The present invention is directed to deconvolution and normalization of assay data. The present invention includes a control and analysis system, used in conjunction with a signal generation and detection apparatus, for capturing, processing and analyzing images of samples having resonance light scattering (RLS) particle labels. The control and analysis system processes instructions and algorithms for performing multiplexed assays of two or more colors, for example, to allow separation and analysis of detected light that contains information from two or more different types or sizes of RLS particles. The multiplexing analysis software is preferably incorporated within the system of the present invention, and the multiplexing analysis is preferably performed in real-time during a scanning or assay procedure. The invention provides for a computer readable medium containing instructions for carrying out the same.

L3: Entry 22 of 53 File: PGPB Jul 24, 2003

DOCUMENT-IDENTIFIER: US 20030139886 A1
TITLE: Method and apparatus for normalization and deconvolution of assay data

Detail Description Paragraph:
[0583] As indicated hereinabove, utilization of RLS detection methods can involve various techniques of data processing, typically utilized for the purpose of

providing such enhancements as greater signal to noise ratios, increased sensitivity, extended dynamic range, comparability within and/or between assays, and to identify particular features. These data processing techniques can be incorporated as sets of instructions embedded in software and/or hardware that is part of an analyzer and/or embedded in a computer with a data connection to an analyzer. Such software is typically recorded in an ordinary computer storage medium, including, but not limited to: volatile or non-volatile random access memory (RAM), read only memory (ROM), magnetic tape, hard or floppy disks, and optical storage media such as compact disks (CD, CD-ROM). Further assay methods, preferably array-based methods and especially microarray assay methods, can advantageously utilize such software and/or hardware.

☐ 23. Document ID: US 20030124589 A1

L3: Entry 23 of 53 File: PGPB Jul 3, 2003

PGPUB-DOCUMENT-NUMBER: 20030124589
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030124589 A1

TITLE: Imaging microarrays

PUBLICATION-DATE: July 3, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Piper, James R.	Aberlady		GB	

US-CL-CURRENT: 435/6; 702/20

ABSTRACT:

A method of obtaining a corrected image of a microarray includes acquiring an image of a microarray including a target spot, and processing the image to correct for background noise and chip misalignment. The method also includes analyzing the image to identify a target patch, edit debris, and correct for ratio bias; and detecting single copy number variation in the target spot using an objective statistical analysis that includes a t-value statistical analysis. The method provides statistically robust computational processes for accurately detecting genomic variation at the single copy level.

L3: Entry 23 of 53 File: PGPB Jul 3, 2003

DOCUMENT-IDENTIFIER: US 20030124589 A1
TITLE: Imaging microarrays

Abstract Paragraph:
A method of obtaining a corrected image of a microarray includes acquiring an image of a microarray including a target spot, and processing the image to correct for background noise and chip misalignment. The method also includes analyzing the image to identify a target patch, edit debris, and correct for ratio bias; and

detecting single copy number variation in the target spot using an objective statistical analysis that includes a t-value statistical analysis. The method provides statistically robust computational processes for accurately detecting genomic variation at the single copy level.

Summary of Invention Paragraph:
[0005] According to one aspect of the invention, a method includes acquiring an image of a genomic microarray including a target spot; processing the image to correct for background noise and chip misalignment; analyzing the image to identify a target patch, edit debris, and correct for ratio bias; and, detecting single copy number variation in the target spot using an objective statistical analysis that includes a t-value statistical analysis. In some embodiments, the target spot is Deoxyribonucleic Acid (DNA). One or more of the following features may also be included.

Summary of Invention Paragraph:
[0010] Further, subsequent to acquiring the image of the genomic microarray and prior to correcting the background noise, processing the image includes automatically detecting misalignment of the genomic microarray and correcting its rotation.

Summary of Invention Paragraph:
[0026] According to another aspect of the invention, a computer program product residing on a computer readable medium causes the processor to acquire an image of a genomic microarray including a target spot; process the image for correcting of a background noise and chip misalignment; analyze the image for identifying a DNA patch, editing of debris, and correcting a ratio bias. The computer program product also causes the processor to detect of single copy number variation in the target spot using an objective statistical analysis.

Summary of Invention Paragraph:
[0029] Subsequent to causing the processor to acquire the image of the genomic microarray and prior to causing the processor to process the image for correcting the background noise, the computer program product further causes the processor to process the image further includes automatically causing the processor to detect misalignment of the genomic microarray and correct rotation of the genomic microarray. The genomic material includes a range between 50 kbp and 200 kbp.

Summary of Invention Paragraph:
[0042] According to another aspect of the invention, a processor and a memory are provided which are configured to acquire an image of a genomic microarray including a target spot; to process the image for correcting of a background noise and chip misalignment; to analyze the image for identifying a DNA patch, editing of debris, and correcting a ratio bias; and, to detect single copy number variation in the target spot using an objective statistical analysis.

Summary of Invention Paragraph:
[0043] According to yet another aspect of the invention, a system includes means for acquiring an image of a genomic microarray including a target spot; means for processing the image for correcting of a background noise and chip misalignment; means for analyzing the image for identifying a DNA patch, editing of debris, and correcting a ratio bias; and, means for detecting single copy number variation in the target spot using an objective statistical analysis.

Summary of Invention Paragraph:
[0052] The methods provide a robust microarray computing system for obtaining data with superior quality and experimental results. Specifically, the image acquisition process provides higher quality images due to improved noise correction mechanisms and tightly integrated hardware and software components. Consequently, higher quality images are examined providing the automated tools a better analytical input

for giving the user more reliable and accurate results. In addition, important experimental results associated with statistical values are provided with a higher degree of confidence.

Detail Description Paragraph:
[0068] As described below, methods and systems of obtaining a corrected image of a microarray include acquiring an image of a microarray including a target spot, processing the image to correct for background noise and chip misalignment, analyzing the image to identify a target patch, edit debris, and correct for ratio bias, and detecting single copy number variation in the target spot using an objective statistical analysis that includes a t-value statistical analysis.

CLAIMS:

1. A method of obtaining a corrected image of a microarray, the method comprising: acquiring an image of a microarray including a target spot; processing the image to correct for background noise and chip misalignment; analyzing the image to identify a target patch, edit debris, and correct for ratio bias; and, detecting single copy number variation in the target spot using an objective statistical analysis that includes a t-value statistical analysis.

9. The method of claim 1, wherein subsequent to acquiring the image of the genomic microarray and prior to correcting for the background noise, processing the image includes automatically detecting misalignment of the genomic microarray and correcting for rotation of the genomic microarray.

29. A computer program product residing on a computer readable medium having instructions stored thereon which; when executed by the processor, cause the processor to: acquire an image of a microarray including a target spot; process the image to correct for background noise and chip misalignment; analyze the image to identify the target patch, edit debris, and correct for ratio bias; and, detect single copy number variation in the target spot using an objective statistical analysis.

32. The computer program product of claim 29, wherein subsequent to causing the processor to acquire the image of the genomic microarray and prior to causing the processor to process the image for correcting the background noise, causing the processor to process the image further includes automatically causing the processor to detect misalignment of the genomic microarray and correct rotation of the genomic microarray.

46. A processor and a memory configured to: acquire an image of a microarray including a target spot; process the image to correct for background noise and chip misalignment; analyze the image to identify a target patch, edit debris, and correct for ratio bias; and, detect single copy number variation in the target spot using an objective statistical analysis.

47. A system comprising: means for acquiring an image of a microarray including a target spot; means for processing the image to correct for background noise and chip misalignment; means for analyzing the image to identify a target patch, edit debris, and correct for ratio bias; and, means for detecting single copy number variation in the target spot using an objective statistical analysis.

☐ 24. Document ID: US 20030087289 A1

L3: Entry 24 of 53 File: PGPB May 8, 2003

PGPUB-DOCUMENT-NUMBER: 20030087289
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030087289 A1

TITLE: Image analysis of high-density synthetic DNA microarrays

PUBLICATION-DATE: May 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Zuzan, Harry	Pleasant Hill	CA	US	
Johnson, Valen E.	Ann Arbor	MI	US	

US-CL-CURRENT: 435/6; 382/128, 702/20

ABSTRACT:

Methods, systems, and computer program products for analyzing images of high density microarray chips analyze the image by estimating background using a blurring kernel and/or a spatial multivariate statistical model of the background. The methods, systems, and computer program products can employ a multivariate statistical model and/or a blurring kernel to obtain more representative hybridization intensity results, particularly for pixels in boundary regions of the probe cells. The methods allow for alternative microarray configurations of nucleic acid probes and do not require the use of mismatch probes and can be independent of the type of nucleotide sequence used. Associated microarrays and systems are also described.

L3: Entry 24 of 53 File: PGPB May 8, 2003

DOCUMENT-IDENTIFIER: US 20030087289 A1
TITLE: Image analysis of high-density synthetic DNA microarrays

Detail Description Paragraph:
[0056] Referring now to FIG. 5, exemplary operations for analyzing an image to account for background illumination and/or noise are illustrated. As shown, an image of an expressed microarray is obtained (block 130). In certain embodiments, to establish the estimated level of background/noise in the image, the extracted raw image data at the resolution of individual pixels can be obtained and analyzed. Still referring to FIG. 5, one or more individual probe cell locations in the image may be positionally estimated in the image as desirable (block 135). The estimates of the probe cell locations may be provided in any suitable manner such as via conventional operations or as described in U.S. Pat. Nos. 6,090,555 and 5,631,734, and co-pending, co-assigned U.S. Provisional Patent Application Serial No. _____ identified by Attorney Docket No. 5405-261PR; the contents of these documents are hereby incorporated by reference as if recited in full herein.

☐ 25. Document ID: US 20030059818 A1

L3: Entry 25 of 53 File: PGPB Mar 27, 2003

PGPUB-DOCUMENT-NUMBER: 20030059818
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030059818 A1

TITLE: Coupled two-way clustering analysis of data

PUBLICATION-DATE: March 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Domany, Eytan	Rehovot		IL	
Getz, Gad	Haifa		IL	
Levine, Erel	Tel Aviv		IL	

US-CL-CURRENT: 435/6; 702/19, 702/20, 707/103R

ABSTRACT:

A novel coupled two-way clustering approach to gene microarray data analysis, for identifying subsets of the genes and samples, such that when one of these items is used to cluster the other, stable and significant partitions emerge. The method of the present invention preferably uses iterative clustering in order to execute this search in an efficient way. This approach is especially suitable for gene microarray data, where the contributions of a variety of biological mechanisms to the gene expression levels are entangled in a large body of experimental data. The method of the present invention was applied to two gene microarray data sets, on colon cancer and leukemia. By identifying relevant subsets of the data and focusing on these subsets, partitions and correlations were found that were masked and hidden when the full data set was used in the analysis.

L3: Entry 25 of 53 File: PGPB Mar 27, 2003

DOCUMENT-IDENTIFIER: US 20030059818 A1
TITLE: Coupled two-way clustering analysis of data

Detail Description Paragraph:
[0051] The coupled two-way clustering method of the present invention is a general way to analyze gene microarray data, and may optionally be used with any suitable clustering algorithm, such that the present invention is not limited to any particular clustering algorithm. A particularly preferred clustering algorithm, which is used in the examples described in greater detail below, is the super-paramagnetic clustering algorithm (SPC) [9, 10, 11, 12]. This algorithm is especially suitable for gene microarray data analysis due to its robustness against noise and its "natural" ability to identify stable clusters.

Detail Description Paragraph:
[0141] The coupled two-way clustering method of the present invention has been demonstrated to be computationally feasible for the cases which were studied. One of the reasons is that the stable clusters generated by the procedure become small with increasing iterations. Therefore their clustering analysis gets faster, and the method typically stops after only a few iterations. The method of the present invention is applicable with any reasonable, suitable choice of clustering algorithm, as long as the selected algorithm is capable of identifying stable

clusters. The examples of analyses which were described above concerned one exemplary but preferred clustering algorithm, which is super-paramagnetic clustering algorithm (SPC). This algorithm is especially suitable for gene microarray data analysis due to its robustness against noise which is inherent in such experiments.

☐ 26. Document ID: US 20030049663 A1

L3: Entry 26 of 53 File: PGPB Mar 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030049663
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030049663 A1

TITLE: Use of reflections of DNA for genetic analysis

PUBLICATION-DATE: March 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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Serina, Lidia	Hamden	CT	US	
Hatchwell, Eli	Cold Spring Harbor	NY	US	

US-CL-CURRENT: 435/6; 435/91.2, 536/23.1

ABSTRACT:

The present invention to provides a solution to problems associated with the use of hybridization for genetic analysis, including but not limited to the use of microarray technology for the analysis DNA. The present invention provides compositions and methods for the use reflections of DNA in genetic analysis. The present invention is also directed to methods for the production of reflections of DNA.

L3: Entry 26 of 53 File: PGPB Mar 13, 2003

DOCUMENT-IDENTIFIER: US 20030049663 A1
TITLE: Use of reflections of DNA for genetic analysis

Detail Description Paragraph:
[0032] The principle of this method is to use the collection of fragments, for example fragments arrayed in a microarray, to isolate the complimentary fragments from a sample for analysis. This creates a sample for hybridization that has a complexity on the order of the array being used for hybridization. By doing this the complexity of the sample can be dropped enormously. This in turn allows for better signal to noise for the probes on the array. This attribute allows the identification of specific fragments from genomes of size and complexity that could not normally be analyzed by conventional methods. The method of the invention can

be used to analyze genome copy number in samples such as human genomic DNA compared on cDNA arrays. Reflection of normal and tumor DNA samples are compared to identify regions of the genome that undergo copy number fluctuation in cancer corresponding to the cDNAs or genes on the array.

☐ 27. Document ID: US 20030044775 A1

L3: Entry 27 of 53 File: PGPB Mar 6, 2003

PGPUB-DOCUMENT-NUMBER: 20030044775
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030044775 A1

TITLE: Technique for quantiating biological markers using quantum resonance interferometry

PUBLICATION-DATE: March 6, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gulati, Sandeep	La Canada Flintridge	CA	US	

US-CL-CURRENT: 435/5; 435/6, 702/20

ABSTRACT:

A technique is described for determining the effectiveness of medical therapy and dosage formulations by analyzing dot spectrograms representative of quantized hybridization activity in biological samples, such as DNA, RNA or other protein biomolecular array samples, taken at different sampling times from a patient undergoing the treatment. The technique directly lends itself to disease progression analysis based on markers such as viral load. In accordance with the technique, a viral diffusion curve associated with a therapy of interest is generated and each dot spectrogram is then mapped to the viral diffusion curve using fractal filtering to yield a filtered viral diffusion curve for each sample. A degree of convergence between the filtered viral diffusion curves is determined. Then, a determination is made as to whether the therapy of interest has been effective by determining whether the degree of convergence increases from one sample to another, with an increase in the degree of convergence being representative of a lack of effectiveness of the therapy of interest. In a specific example described herein, the viral diffusion curve is generated by inputting parameters representative of viral load studies for the therapy of interest, generating a preliminary viral diffusion curve based upon the viral load studies and then calibrating a degree of directional causality in the preliminary viral diffusion curve to yield the viral diffusion curve. Each dot spectrogram is mapped to the viral diffusion curve using fractal filtering by generating a partitioned iterated fractal system (IFS) model representative of the dot spectrogram, determining affine parameters for IFS model, and then mapping the dot spectrogram onto the viral diffusion curve using the IFS. Before the dot spectrogram is mapped to the viral diffusion curve, the dot spectrogram is interferometrically enhanced. After the mapping, any uncertainty in the filtered viral diffusion curve is compensated for using non-linear information filtering. A method is also described

for determining the viral load within a biological sample by analyzing a dot spectrogram generated for the sample in connection with viral diffusion curves associated with a therapy of interest. Thus a technique is provided for detecting and tracking infections such as viral infections and establishing clinical endpoints, based on accurate biomolecular measurements of viral DNA or RNA in peripheral blood. The technique also provides a computational protocol for leveraging a clinical marker to establish and track therapy effectiveness based on quantification of amplified nucleic acid i.e., DNA and RNA assays. The technique can potentially amplify dynamic ranges over 100.times. or more over conventional assays. The technique enables point-of-care viral load detection biosensors to reliably predict the likelihood of disease progression and thereby allows the patient to make earlier and more effective decisions about treatment.

L3: Entry 27 of 53 File: PGPB Mar 6, 2003

DOCUMENT-IDENTIFIER: US 20030044775 A1
TITLE: Technique for quantiating biological markers using quantum resonance interferometry

Detail Description Paragraph:
[0190] Specifically, we include the dynamic NIF correction function to the gradient of the VDC at the sample point normalized in a manner such that when the information uncertainty is null, the correction term vanishes. As discussed in the above steps, the NIF correction terms is actually derived from the noise statistics of the microarray sample.

☐ 28. Document ID: US 20030033290 A1

L3: Entry 28 of 53 File: PGPB Feb 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030033290
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030033290 A1

TITLE: Program for microarray design and analysis

PUBLICATION-DATE: February 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Garner, Harold R.	Flower Mound	TX	US	
Kulkarni, Amit	Dallas	TX	US	

US-CL-CURRENT: 707/3

ABSTRACT:

The invention relates to computer-based systems and methods for the design, comparison and analysis of genetic and proteomic databases. In a particular embodiment, the recited systems and methods have been implemented in a computer tool called ARROGANT. ARROGANT, in the analysis mode, is a comprehensive tool for

providing annotation to large gene and protein collections. ARROGANT takes in a large collection of sequence identifiers and associates it with other information collected from many sources like sequence annotations, pathways, homology, polymorphisms, artifacts, etc. The simultaneous annotation for a large assembly of genes makes the collection of genomic/EST sequences truly informative.

L3: Entry 28 of 53 File: PGPB Feb 13, 2003

DOCUMENT-IDENTIFIER: US 20030033290 A1
TITLE: Program for microarray design and analysis

Summary of Invention Paragraph:
[0008] The production of DNA microarrays can be divided into four stages: a. Selection of array elements and design of the probe DNA; b. Preparation of the probe DNA; c. Preparation of a suitable design substrate to spot the probes on; d. Deposition of array elements. The selection of array elements for microarrays involves assembling a large gene collection. It would be very valuable if the same tool (to compile a large gene collection) could be used to further design primers, look for commercially available clones (expression microarrays) and design resequencing probes (resequencing microarrays). Once the genes are spotted on the microarray and hybridized to fluorescent labeled probes, there are a number of software programs that help in conversion of the fluorescence of the scanned image to numbers, using complex mathematical corrections to extract signal from background noise. e.g. Genepix (http://www.axon.com/GN_GenePixSoftware.html) and ArrayVision (http://imaging.brocku.ca/products/Arrayvision.htm). These numbers indicate level of expression. Other programs such as GeneSpring (Silva et al, HMS Beagle: The BioMedNet Magazine Issue 82, 2000), Cluster Treeview (Eisen M B et al, Proc Natl Acad Sci USA 95) and Spotfire (http://www.spotfire.com), help in the analysis by clustering the data together using various methods based on K-means, hierarchal or self-organizing maps. Clustering algorithms use the expression level data to group the various elements on the array. It would also be very useful to view the elements of the array with their complete annotation and overlay the expression level data on top of it. The data could further be selectively viewed by sorting on various annotation fields and the expression level data. This approach could be useful to view any large gene collection in general. With the increasing number of microarray experiments, it would be valuable to compare elements between different microarrays considering that fragments of the same gene might be represented by different sequence identifiers. For example, two different accession numbers might belong to the same UniGene cluster, representing the same gene. An artifact sometimes observed in the results obtained from an expression profiling microarray experiment is that some sequences might hybridize to other sequences to which they are significantly similar. This leads to false positive results after a microarray experiment. Although Human Cot DNA is often used to prevent non-specific hybridization by blocking simple repetitive elements in genomic DNA, as shown in experiments to study cross-hybridization, Human Cot DNA is not very effective in preventing cross hybridization. ARROGANT computationally estimates the amount of cross hybridization for each sequence and tags potential genes as possible candidates for cross hybridization.

☐ 29. Document ID: US 20030013109 A1

L3: Entry 29 of 53 File: PGPB Jan 16, 2003

PGPUB-DOCUMENT-NUMBER: 20030013109
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030013109 A1

TITLE: Hairpin sensors using quenchable fluorescing agents

PUBLICATION-DATE: January 16, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ballinger, Clinton T.	Burnt Hills	NY	US	
LoCascio, Michael	Albany	NY	US	
Landry, Daniel P.	Clifton Park	NY	US	

US-CL-CURRENT: 435/6; 435/287.2

ABSTRACT:

The present invention provides for a device and method for detecting genetic material. The device includes at least one hairpin sensor or, preferably two or more hairpin sensors, spatially and/or spectrally multiplexed on a conductive or semi-conductive substrate or particle. The at least one hairpin sensor includes a quenchable fluorescing agent bound to a hairpin loop assembly and the hairpin loop assembly includes a probe complementary to a nucleotide sequence of interest. The method includes providing at least one hairpin sensor, exposing the at least one hairpin sensor to a sample of interest, and detecting fluorescence produced by the quenchable fluorescing agent. The fluorescence indicates the binding of a target nucleotide sequence to the complementary probe of the hairpin loop assembly.

L3: Entry 29 of 53 File: PGPB Jan 16, 2003

DOCUMENT-IDENTIFIER: US 20030013109 A1
TITLE: Hairpin sensors using quenchable fluorescing agents

Summary of Invention Paragraph:
[0008] The biochip industry has recently started using miniaturization and integration, similar to computer chip manufacturers, to develop entire assay systems on a single support. These microarrays or "labs on a chip" have been used to revolutionize genomics, drug development, clinical diagnostics and environmental monitoring in much the same way microprocessors revolutionized the computer industry. These microarrays give higher throughput, lower cost, portability and automation than the traditional bio-chemical assay methods. Because these biochips often have used traditional fluorescing dyes, however, they have allowed for only limited spectral multiplexing because of the high background noise and broad emission spectra, for example, of fluorescing dyes. Further, prior microarrays have provided limited spatial multiplexing as the number of molecules that can be identified in a single assay is limited by the number of differentiable locations on the array.

☐ 30. Document ID: US 20020169562 A1

L3: Entry 30 of 53 File: PGPB Nov 14, 2002

PGPUB-DOCUMENT-NUMBER: 20020169562
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020169562 A1

TITLE: Defining biological states and related genes, proteins and patterns

PUBLICATION-DATE: November 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Stephanopoulos, Gregory	Chester	MA	US	
Misra, Jatin	Cambridge	MA	US	
Hwang, Daehee	Cambridge	MA	US	
Schmitt, William A. JR.	Boston	MA	US	
Alevizos, Ilias	Watertown	MA	US	
Silva, Saliya Sudharshana	Kandy	CO	LK	
Gill, Ryan T.	Boulde		US	

US-CL-CURRENT: 702/19; 435/6, 530/350, 536/23.1

ABSTRACT:

Disclosed are a variety of methods and computer systems for use in the analysis of gene and protein expression data. Also disclosed are methods for the definition of the cellular state of cells and tissues from multidimensional physiological data such as those obtained from gene expression measurements with DNA microarrays. A variety of classification methods can be applied to expression data to achieve this goal. Demonstrated is the application of several statistical tools including Wilks' lambda ratio of within-group to total variance, Fisher Discriminant Analysis, and the misclassification error rate to the identification of discriminating genes and the overall classification of expression data. Examples from several different cases demonstrate the ability of the method to produce well-separated groups in the projection space representing distinct physiological states. The method can be augmented and is useful in disease diagnosis, drug screening and bioprocessing applications.

L3: Entry 30 of 53 File: PGPB Nov 14, 2002

DOCUMENT-IDENTIFIER: US 20020169562 A1
TITLE: Defining biological states and related genes, proteins and patterns

Detail Description Paragraph:
[0301] We applied FDA projections to four examples of gene expression phenotypes generated in our laboratory and also published in the literature. In the first example, cultures of the photosynthetic bacterium Synechocystis sp. PCC 6803 were cultivated through an initial period of 48 hours of growth under light followed by 24 hours of darkness. The cultures where then cycled between light and dark conditions for 100 minutes each (FIG. 4). The expression levels of 88 genes associated with harvesting of light energy and central carbon metabolism were measured at 23 time points (29 total samples, including duplicates) using DNA microarrays. Gill, R. T., E. Katsoulakis, W. Schmitt, G. Taroncher-Oldenburg and G. Stephanopoulos, "Dynamic transcriptional profiling of the light to dark transition

in Synechocystis sp. PCC6803," (submitted) (2000). Total signal to noise ratio of the microarray fluorescence was determined to be c.a. 4.0 indicating that background noise minimally interfered with the fluorescence of hybridized spots. Reproducibility of expression measurements, evaluated from microarray to microarray measurements, as well as from intra-microarray triplicate spots, was 45% suggesting that a 90% difference in fluorescence is reproducible within 95% confidence level Of the 88 total genes considered, 27 discriminatory genes were identified based on their Wilks' lambda measure with a stringent 99% confidence level. Dillon, W.R., and M. Goldstein. Multivariate Analysis, John Wiley & Sons (1984). FIG. 4 shows the projection of the expression phenotype of the 27 Synechocystis discriminatory genes to the FDA-defined 3-D space. Three dimensions were used in this projection to distinguish the four phenotypic classes of growth under the light and dark conditions shown in FIG. 4. The class separation can also be seen in 2-D diagrams of the above canonical variables (FIG. 4c). CVI distinguishes group 2 from the other groups while CV2 separates groups I and 3. Hence, the second CV loadings provide information on the identity of the genes supporting the differences in the cellular processes occurring under light and dark conditions.

☐ 31. Document ID: US 20020155480 A1

L3: Entry 31 of 53 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020155480
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020155480 A1

TITLE: Brain tumor diagnosis and outcome prediction

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Golub, Todd R.	Newton	MA	US	
Lander, Eric S.	Cambridge	MA	US	
Pomeroy, Scott	Newton	MA	US	
Tamayo, Pablo	Cambridge	MA	US	

US-CL-CURRENT: 435/6

ABSTRACT:

Methods for predicting phenotypic classes of brain tumors, such as brain tumor type or treatment outcome, for brain tumor samples based on gene expression profiles are described.

L3: Entry 31 of 53 File: PGPB Oct 24, 2002

DOCUMENT-IDENTIFIER: US 20020155480 A1
TITLE: Brain tumor diagnosis and outcome prediction

Detail Description Paragraph:
[0069] Data Analysis: Supervised Learning. Genes correlated with particular class distinctions (e.g., classic vs. desmoplastic medulloblastoma) were identified by sorting all of the genes on the array according the signal-to-noise statistic (.mu..sub.0-.mu..sub.1)/(.sigma..- sub.0+.sigma..sub.1), where .mu. and .sigma. represent the median and standard deviation of expression, respectively, for each class. Similar results were obtained using a standard t-statistic as the metric ((.mu..sub.0-.mu..sub.1)/sqrt(.sigma..sub.0.sup.2/N0+.sigma..sub.1.sup.2/-N.sub.1)), where N represents the number of samples in each class (see Supplementary Information; http://www.genome.wi.mit.edu/MPR/CNS). Permutation of the column (sample) labels was performed to compare these correlations to what would be expected by chance in 99% of the permutations. For classification, a modification of the k-NN algorithm was developed that predicts the class of a new data point by calculating the Euclidean distance (d) of the new sample to the k nearest samples (for these experiments, k=5) in the training set using normalized gene expression data, and selecting the class to be that of the majority of the k samples. The weight given to each neighbor was 1/d. The k-NN models were evaluated by 60-fold leave-one-out cross-validation whereby a training set of 59 samples was used to predict the class of a randomly withheld sample, and the cumulative error rate was recorded. Models with variable numbers of genes (1-200, selected according to their correlation with the survivor vs. treatment failure distinction in the training set) were tested in this manner. An 8-gene k-NN outcome prediction model yielded the lowest error rate, and was therefore used to generate Kaplan-Meier survival plots using S-Plus. Predictors using metastatic staging or TrkC were constructed by finding the decision boundary half way between the classes: (.mu..sub.class0+.mu..sub.class1)/2 using either the staging values 0 vs. 1, 2, 3, 4 or the continuous TrkC microarray gene expression levels, and then predicting the unknown sample according to its location with respect to that boundary.

☐ 32. Document ID: US 20020097900 A1

L3: Entry 32 of 53 File: PGPB Jul 25, 2002

PGPUB-DOCUMENT-NUMBER: 20020097900
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020097900 A1

TITLE: System for the automatic analysis of images such as DNA microarray images

PUBLICATION-DATE: July 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Arena, Paolo	Catania		IT	
Fortuna, Luigi	Siracusa		IT	
Lavorgna, Mario	Bacoli		IT	
Occhipinti, Luigi	Ragusa		IT	

US-CL-CURRENT: 382/129

ABSTRACT:

The system can be used for the automatic analysis of images (I), comprising a matrix of spots, such as images of DNA microarrays after hybridisation. The system can be associated--and preferably integrated in a single monolithic component implementing VLSI CMOS technology--to a sensor (10) for acquiring said images (I). The system comprises a circuit (20) for processing the signals corresponding to the images (I), configured according to a cellular neural network (CNN) architecture for the parallel analogue processing of signals.

L3: Entry 32 of 53 File: PGPB Jul 25, 2002

DOCUMENT-IDENTIFIER: US 20020097900 A1
TITLE: System for the automatic analysis of images such as DNA microarray images

Brief Description of Drawings Paragraph:
[0047] FIG. 8 (which is split into two parts, identified by 8a and 8b, respectively) and figures from 9 to 12 illustrate, for example, the method according to which the various operations concerning filtering, segmenting, and the morphological operations, which can be implemented in a system according to this invention, can be conducted to isolate useful information with respect to the various sources of noise which could lead to false interpretations of the results during the automatic microarray image analysis process.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 33. Document ID: US 20020090620 A1

L3: Entry 33 of 53 File: PGPB Jul 11, 2002

PGPUB-DOCUMENT-NUMBER: 20020090620
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020090620 A1

TITLE: Identification of drugs and drug targets by detection of the stress response

PUBLICATION-DATE: July 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Davis, Ronald W.	Palo Alto	CA	US	
Giaever, Guri N.	Palo Alto	CA	US	

US-CL-CURRENT: 435/6; 435/32, 435/4

ABSTRACT:

The invention features methods of high throughput screening of candidate drug agents and rapid identification of drug targets by examining induction of the stress response in a host cell, e.g., the stress response in wildtype host cells and/or in host cells that differ in target gene product dosage (e.g., host cells that have two copies of a drug target gene product-encoding sequence relative to one copy). In general, induction of the stress response in wildtype host cells indicates that a candidate agent has activity of the drug. Induction of a relatively lower or undetectable stress response in a host cell comprising an

alteration in gene product dosage indicates that the host cell is drug-sensitive and is altered in a gene product that plays a role in resistance to the drug.

L3: Entry 33 of 53 File: PGPB Jul 11, 2002

DOCUMENT-IDENTIFIER: US 20020090620 A1
TITLE: Identification of drugs and drug targets by detection of the stress response

Summary of Invention Paragraph:
[0019] Another advantage of the invention is that the methods of the invention exploit the stress response, which is normally regarded as unavoidable "background noise," to rapidly identify candidate agents having drug activity and, where desired, identify the target gene products of the drug activity. Importantly, this stress response often clouds interpretation of microarray expression experiments, forcing the sensitivity to be lowered. The present invention exploits the robust stress response of cells to provide a sensitive metric of drug effectiveness.

☐ 34. Document ID: US 20020081610 A1

L3: Entry 34 of 53 File: PGPB Jun 27, 2002

PGPUB-DOCUMENT-NUMBER: 20020081610
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020081610 A1

TITLE: Assays and materials for embryonic gene expression

PUBLICATION-DATE: June 27, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hemmati-Brivanlou, Ali	New York	NY	US	
Altmann, Curtis R.	New York	NY	US	

US-CL-CURRENT: 435/6; 435/287.2, 536/24.3

ABSTRACT:

The present invention relates to methods for detecting differential expression of embryonic gene products known to play a fundamental role in the embryonic developmental process using nucleic acid arrays containing Xenopus embryonic gene sequences as set forth in Appendix 1. This allows the detection of the expression of differentially expressed genes in embryonic cells, for diagnosing developmental disorders or identifying different types of embryonic cells.

L3: Entry 34 of 53 File: PGPB Jun 27, 2002

DOCUMENT-IDENTIFIER: US 20020081610 A1
TITLE: Assays and materials for embryonic gene expression

Detail Description Paragraph:
[0131] Because the clones selected for RT-PCR analysis in these experiments were detected at much lower levels than are detected at much lower levels than the genes analyzed in Example 4, above, and therefore have a lower signal intensity on microarrays, background noise is a greater factor in analyzing the data. Thus, analysis of total cellular mRNA using the microarrays of this invention are useful for identifying candidate genes whose expression is spatially restricted in early vertebrate embryos. Such candidate genes can then be confirmed, e.g., using more sensitive methods such as the RT-PCR techniques described here, by hybridizing polyA.sup.+ RNA samples from cells to microarrays, or by using microarrays with more specific and sensitive probes for these candidate genes.

☐ 35. Document ID: US 20020037149 A1

L3: Entry 35 of 53 File: PGPB Mar 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020037149
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020037149 A1

TITLE: Fiber optic scanner

PUBLICATION-DATE: March 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chen, Shiping	Rockville	MD	US	

US-CL-CURRENT: 385/147

ABSTRACT:

The disclosed scanning structure includes an apparatus for light delivery and light receiving from a light-excitable area on a substrate to be measured by the scanning structure. The light delivery and receiving apparatus may include an optical fiber having a proximal end and a distal end which transmits light having a certain wavelength or light with several varying wavelengths to excite the substrate samples. This optical fiber may also simultaneously receive light which may be emitted by fluorescing samples on the substrate. The scanning structure also may further include a holder for the optical fiber that is able to transverse variable distances over the substrate to be measured or examined. Holders may include galvano scanners as well as resonating suspension beams. A light source, e.g., a laser, may be optically coupled to the optic fiber's proximal end. And this light source may be of a certain wavelength, but multiple light sources each having a different wavelength may also be used simultaneously by coupling the light sources into either a single optic fiber through wavelength multiplexers or by placing individual optic fibers carrying differing wavelengths in close proximity to each other. As the light is transmitted down to the substrate through the optic fiber, the fiber is sufficiently close to the substrate microarray so that it can also receive the emitted fluorescing light.

L3: Entry 35 of 53 File: PGPB Mar 28, 2002

DOCUMENT-IDENTIFIER: US 20020037149 A1
TITLE: Fiber optic scanner

Summary of Invention Paragraph:
[0007] In the CCD based system, the imager and lens are both the main cost drivers. Here, the excitation light is expanded to a large area causing a great reduction in energy density. The exposure time has to be extended several tens of seconds to compensate for this reduction. Because of the long exposure time, the CCD imager has to be cooled to maintain a reasonable single to noise ratio. Such a cooled, large format CCD imager is very expensive at present. In addition, the optical lens in the system has to be corrected for chromatic aberrations and image distortions over a large field of view, which significantly increases its cost in comparison to the lens in the point-to-point system in a scanning microscope. Furthermore, there is currently no CCD imager with sufficient resolution and format to cover the entire area of a slide (25 mm.times.75 mm). Mechanical scanning is still required for CCD based systems, which reduces the speed of the reader. At present, most microarray readers on the market require 5 minutes or more to complete the scanning of a 25 mm.times.70 mm slide, which is too slow for many applications.

☐ 36. Document ID: US 20020019704 A1

L3: Entry 36 of 53 File: PGPB Feb 14, 2002

PGPUB-DOCUMENT-NUMBER: 20020019704
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020019704 A1

TITLE: Significance analysis of microarrays

PUBLICATION-DATE: February 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Tusher, Virginia Goss	Palo Alto	CA	US	
Tibshirani, Robert	Palo Alto	CA	US	
Chu, Gilbert	Palo Alto	CA	US	

US-CL-CURRENT: 702/19

ABSTRACT:

Microarrays can measure the expression of thousands of genes and thus identify changes in expression between different biological states. Methods are needed to determine the significance of these changes, while accounting for the enormous number of genes. We describe a new method, Significance Analysis of Microarrays (SAM), that assigns a score to each gene based on the change in gene expression relative to the standard deviation of repeated measurements. For genes with scores greater than an adjustable threshold, SAM uses permutations of the repeated measurements to estimate the percentage of such genes identified by chance, the false discovery rate (FDR). When the transcriptional response of human cells to

ionizing radiation was measured by microarrays, SAM identified 34 genes that changed at least 1.5-fold with an estimated FDR of 12%, compared to FDRs of 60% and 84% using conventional methods of analysis. Of the 34 genes, 19 were involved in cell cycle regulation, and 3 in apoptosis. Surprisingly, 4 nucleotide excision repair genes were induced, suggesting that this repair pathway for UV-damaged DNA might play a heretofore unrecognized role in repairing DNA damaged by ionizing radiation.

L3: Entry 36 of 53 File: PGPB Feb 14, 2002

DOCUMENT-IDENTIFIER: US 20020019704 A1
TITLE: Significance analysis of microarrays

Detail Description Paragraph:
[0062] As noted above, factors inherent in the process of acquisition of microarray data itself may introduce noise that renders it difficult to discover the significance of differences in gene expression or other biological behavior or falsely identify genes to be of statistical significance. To overcome such problem, a number of methods are described above which allow full utilization of the microarray data. One difficulty in making use of the microarray data is due to the fact that the expression levels of the genes have a wide range of values or scattered values. It is, therefore, desirable to adjust the parameter d(i) so that it is essentially independent of the wide variation of the values of the parameter d(i) and/or of the scatter value s(i). After the parameter has been so adjusted, then all of the data can be fully utilized.

☐ 37. Document ID: US 20020009744 A1

L3: Entry 37 of 53 File: PGPB Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020009744
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020009744 A1

TITLE: In-line complete spectral fluorescent imaging of nucleic acid molecules

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Bogdanov, Valery	Baltimore	MD	US	

US-CL-CURRENT: 435/6; 356/319, 356/326

ABSTRACT:

The present invention provides a hyperspectral imaging apparatus and methods for employing such an apparatus for multi-dye/base detection of a nucleic acid molecule coupled to a solid surface.

L3: Entry 37 of 53 File: PGPB Jan 24, 2002

DOCUMENT-IDENTIFIER: US 20020009744 A1
TITLE: In-line complete spectral fluorescent imaging of nucleic acid molecules

Detail Description Paragraph:
[0046] The present invention offers a significant advantage over traditional gel-based mutation detection methods in the areas of through-put, cost, reliability and operational simplicity. The present invention can accurately identify heterozygous mutations. Preferably, analysis of both strands is performed to reduce potential mis-calling. Under another preferred embodiment, genotyping of wild type DNA (as a reference strand) for comparison of background noise levels is performed to improve the ability to accurate identify "true" heterozygotes. The present invention can be used to detect the incorporation of labeled dye terminators either in solution, or on microarrays.

☐ 38. Document ID: US 6704662 B2

L3: Entry 38 of 53 File: USPT Mar 9, 2004

US-PAT-NO: 6704662
DOCUMENT-IDENTIFIER: US 6704662 B2

TITLE: Technique for quantiating biological markers using quantum resonance interferometry

DATE-ISSUED: March 9, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gulati; Sandeep	La Canada Flintridge	CA		

US-CL-CURRENT: 702/27; 422/82.05, 435/6, 435/91.1, 435/91.2, 712/200

ABSTRACT:

A technique is described for quantitating biological indicators, such as viral load, using interferometric interactions such as quantum resonance interferometry. A biological sample is applied to an array information structure that has a plurality of elements that emit data indicative of viral load. A digitized output pattern of the arrayed information structure is interferometrically enhanced by generating interference between the output pattern and a reference wave. The interferometrically enhanced output pattern is then analyzed to identify emitted data indicative of viral load which in turn is used to determine viral load.

21 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

L3: Entry 38 of 53 File: USPT Mar 9, 2004

DOCUMENT-IDENTIFIER: US 6704662 B2

TITLE: Technique for quantiating biological markers using quantum resonance interferometry

Detailed Description Text (167):
Specifically, we include the dynamic NIF correction function to the gradient of the VDC at the sample point normalized in a manner such that when the information uncertainty is null, the correction term vanishes. As discussed in the above steps, the NIF correction terms is actually derived from the noise statistics of the microarray sample.

☐ 39. Document ID: US 6671625 B1

L3: Entry 39 of 53 File: USPT Dec 30, 2003

US-PAT-NO: 6671625
DOCUMENT-IDENTIFIER: US 6671625 B1

TITLE: Method and system for signal detection in arrayed instrumentation based on quantum resonance interferometry

DATE-ISSUED: December 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gulati; Sandeep	La Canada	CA		

US-CL-CURRENT: 702/20; 435/6, 435/7.1, 702/19, 702/27

ABSTRACT:

A technique is disclosed that is useful for determining the presence of specific hybridization expression within an output pattern generated from a digitized image of a biological sample applied to an arrayed platform. The output pattern includes signals associated with noise, and signals associated with the biological sample, some of which are degraded or obscured by noise. Signal processing, such as interferometry, or more specifically, resonance interferometry, and even more specifically quantum resonance interferometry or stochastic resonance interferometry, is used to amplify signals associated with the biological sample having an intensity lower than the intensity of signals associated with noise so that they may be clearly distinguished from background noise. The improved detection technique allows rapid, reliable, and inexpensive measurements of arrayed platform output patterns.

24 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

L3: Entry 39 of 53 File: USPT Dec 30, 2003

DOCUMENT-IDENTIFIER: US 6671625 B1
TITLE: Method and system for signal detection in arrayed instrumentation based on

quantum resonance interferometry

Brief Summary Text (9):
Accordingly, it would highly desirable to provide an improved method and apparatus for analyzing the output of the DNA microarray to more expediently, reliably, and inexpensively determine the presence of any medical conditions or concerns within the patient providing the DNA sample. It is particularly desirable to provide a technique that can identify mutation signatures within dot spectrograms even in circumstance wherein the signal to noise ration is extremely low. It is to these ends that aspects of the invention are generally drawn.

☐ 40. Document ID: US 6633659 B1

L3: Entry 40 of 53 File: USPT Oct 14, 2003

US-PAT-NO: 6633659
DOCUMENT-IDENTIFIER: US 6633659 B1

TITLE: System and method for automatically analyzing gene expression spots in a microarray

DATE-ISSUED: October 14, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zhou; Yi-Xiong	Los Angeles	CA		

US-CL-CURRENT: 382/129; 435/6, 702/21

ABSTRACT:

A digital image processing-based system and method are disclosed for quantitatively assessing nucleic acid species expressed in a microarray. The microarray is a grid of a plurality of sub-grids of the nucleic acid species. The system includes a scanner that has a digital scanning sensor that-scans the microarray and transmits from an output a digital image of the microarray, and a computer that receives the digital image of the microarray from the scanner and then processes the digital image, detecting an expression signal of the nucleic acid species, segmenting the expression signal, calculating a measure of the segmented expression signal, and providing the measure at the output of the computer. Prior to segmenting the expression signal for a nucleic acid species, the expression signal is characterized by a center pixel in the digital image and an approximate radius around the center pixel. The computer segments the expression signal by (a) tentatively classifying pixels within the approximate radius as signal pixels and those outside the approximate radius as background pixels, (b) determining major intensity modes for the signal pixels and for the background pixels, and (c) using the major intensity modes, reclassifying the signal and background pixels depending on each pixel's intensity relative to the major intensity modes.

62 Claims, 20 Drawing figures
Exemplary Claim Number: 1

Number of Drawing Sheets: 14

L3: Entry 40 of 53 File: USPT Oct 14, 2003

DOCUMENT-IDENTIFIER: US 6633659 B1
TITLE: System and method for automatically analyzing gene expression spots in a microarray

Detailed Description Text (20):
After the spatial region for each sub-grid has been partitioned, the automatic sub-grid detection process 501 proceeds to identify, as shown in FIG. 7, the rows and columns for each sub-grid of step 702. Again, the steps to find the rows in a sub-grid are preferably essentially the same as the steps for finding the columns. Thus, only the process for identifying columns in a sub-grid is outlined below. FIG. 9 depicts steps for a preferred row/column detection process 702. In the first step 900, all of the pixels in a sub-grid region along the vertical dimension are summed to form a one-dimensional horizontal vector. Next, an "averaging" or low pass filter whose width is equal to the expected diameter of the spots is applied to the vector in step 902. This averaging step 902 is performed because the image of each sub-grid region is smaller than the overall microarray image that was processed in the previous sub-grid region-locating step 700. By applying the averaging filter, the noise that is inherent in a typical microarray image is reduced. Next, the maxima or peaks in the horizontal vector are determined in step 904, again using a maximum filter in which the size of the maximum filter is preferably equal to the expected spot size. In the next step 906, using the previously calculated mode distance M to establish additional peak locations, peaks are added to the vector to fill the length of the sub-grid region. The resulting peak locations specify the locations of the columns in the sub-grid region. The previous steps for detecting the columns in a sub-grid region are repeated 908 to determine the locations of the rows in the sub-grid or vice versa. Finally, a check step 910 is performed to determine whether the number of peaks for each vector is at least as high as expected. For the horizontal vectors, the number of peaks should equal or be greater than the expected number of columns in a sub-grid. For vertical vectors, the number of peaks should be equal to or greater than the number of rows in a sub-grid. If the number of peaks is less than expected for a horizontal or vertical vector, then the process exits at step 912, having not performed successfully. If the number of peaks for a given vector is equal to or greater than the expected number, then the process exits at step 914 with the row and column detection process 702 being considered successful. With a successful completion of this process, the rows and columns define candidate sub-grids with grid-point intersections in each sub-grid region of the microarray.

☐ 41. Document ID: US 6495363 B2

L3: Entry 41 of 53 File: USPT Dec 17, 2002

US-PAT-NO: 6495363
DOCUMENT-IDENTIFIER: US 6495363 B2

TITLE: In-line complete spectral fluorescent imaging of nucleic acid molecules

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bogdanov; Valery	Baltimore	MD		

US-CL-CURRENT: 435/287.2; 435/6, 435/7.1, 435/91.2, 536/22.1, 536/23.1, 536/24.3, 536/24.31, 536/24.32, 536/24.33

ABSTRACT:

The present invention provides a hyperspectral imaging apparatus and methods for employing such an apparatus for multi-dye/base detection of a nucleic acid molecule coupled to a solid surface.

10 Claims, 8 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 7

L3: Entry 41 of 53 File: USPT Dec 17, 2002

DOCUMENT-IDENTIFIER: US 6495363 B2
TITLE: In-line complete spectral fluorescent imaging of nucleic acid molecules

Detailed Description Text (4):
The present invention offers a significant advantage over traditional gel-based mutation detection methods in the areas of through-put, cost, reliability and operational simplicity. The present invention can accurately identify heterozygous mutations. Preferably, analysis of both strands is performed to reduce potential mis-calling. Under another preferred embodiment, genotyping of wild type DNA (as a reference strand) for comparison of background noise levels is performed to improve the ability to accurate identify "true" heterozygotes. The present invention can be used to detect the incorporation of labeled dye terminators either in solution, or on microarrays.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 42. Document ID: US 6245511 B1

L3: Entry 42 of 53 File: USPT Jun 12, 2001

US-PAT-NO: 6245511
DOCUMENT-IDENTIFIER: US 6245511 B1
**** See image for Certificate of Correction ****

TITLE: Method and apparatus for exponentially convergent therapy effectiveness monitoring using DNA microarray based viral load measurements

DATE-ISSUED: June 12, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gulati; Sandeep	La Canada	CA	91011	

US-CL-CURRENT: 435/6; 435/91.2, 536/24.3

ABSTRACT:

A technique is described for determining the effectiveness of medical therapy and dosage formulations by analyzing dot spectrograms representative of quantized hybridization activity in biological samples, such as DNA, RNA, or other protein biomolecular array samples, taken at different times from a patient undergoing the medical therapy. This technique enables disease progression analysis based on surrogate markers such as viral load. In accordance with the technique, a viral diffusion curve associated with a therapy of interest is generated and each dot spectrogram is then mapped to a viral diffusion curve using fractal filtering. Next, degree of convergence towards the peak of VDC, between the sample points on a filtered viral diffusion curve is determined. The technique allows for point-of-care viral load detection biosensors to accurately and reliably predict the likelihood of disease progression.

46 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

L3: Entry 42 of 53 File: USPT Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6245511 B1
**** See image for Certificate of Correction ****
TITLE: Method and apparatus for exponentially convergent therapy effectiveness monitoring using DNA microarray based viral load measurements

Detailed Description Text (173):
Specifically, we include the dynamic NIF correction function to the gradient of the VDC at the sample point normalized in a manner such that when the information uncertainty is null, the correction term vanishes. As discussed in the above steps, the NIF correction terms is actually derived from the noise statistics of the microarray sample.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. D

☐ 43. Document ID: US 6245507 B1

L3: Entry 43 of 53 File: USPT Jun 12, 2001

US-PAT-NO: 6245507
DOCUMENT-IDENTIFIER: US 6245507 B1

TITLE: In-line complete hyperspectral fluorescent imaging of nucleic acid molecules

DATE-ISSUED: June 12, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bogdanov; Valery	Baltimore	MD		

US-CL-CURRENT: 435/6; 204/450, 204/461, 356/300, 356/301, 356/302, 356/303,

356/344, 435/91.1, 435/91.2, 536/24.3, 536/24.31, 536/24.33

ABSTRACT:

The present invention provides a hyperspectral imaging apparatus and methods for employing such an apparatus for multi-dye/base detection of a nucleic acid molecule coupled to a solid surface.

14 Claims, 8 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 7

L3: Entry 43 of 53 File: USPT Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6245507 B1
TITLE: In-line complete hyperspectral fluorescent imaging of nucleic acid molecules

Detailed Description Text (4):
The present invention offers a significant advantage over traditional gel-based mutation detection methods in the areas of through-put, cost, reliability and operational simplicity. The present invention can accurately identify heterozygous mutations. Preferably, analysis of both strands is performed to reduce potential mis-calling. Under another preferred embodiment, genotyping of wild type DNA (as a reference strand) for comparison of background noise levels is performed to improve the ability to accurate identify "true" heterozygotes. The present invention can be used to detect the incorporation of labeled dye terminators either in solution, or on microarrays.

☐ 44. Document ID: US 6142681 A

L3: Entry 44 of 53 File: USPT Nov 7, 2000

US-PAT-NO: 6142681
DOCUMENT-IDENTIFIER: US 6142681 A

TITLE: Method and apparatus for interpreting hybridized bioelectronic DNA microarray patterns using self-scaling convergent reverberant dynamics

DATE-ISSUED: November 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gulati; Sandeep	La Canada	CA		

US-CL-CURRENT: 702/19; 382/129, 435/287.2, 435/288.7, 435/6, 435/71.1, 435/91.1, 436/173, 536/25.3, 536/25.4, 702/20

ABSTRACT:

A technique is described for identifying mutations, if any, present in a biological sample, from a pre-selected set of known mutations. The method can be applied to

DNA, RNA and peptide nucleic acid (PNA) microarrays. The method analyzes a dot spectrogram representative of quantized hybridization activity of oligonucleotides in the sample to identify the mutations. In accordance with the method, a resonance pattern is generated which is representative of nonlinear resonances between a stimulus pattern associated with the set of known mutations and the dot spectrogram. The resonance pattern is interpreted to a yield a set of confirmed mutations by comparing resonances found therein with predetermined resonances expected for the selected set of mutations. In a particular example, the resonance pattern is generated by iteratively processing the dot spectrogram by performing a convergent reverberation to yield a resonance pattern representative of resonances between a predetermined set of selected Quantum Expressor Functions and the dot spectrogram until a predetermined degree of convergence is achieved between the resonances found in the resonance pattern and resonances expected for the set of mutations. The resonance pattern is analyzed to a yield a set of confirmed mutations by mapping the confirmed mutations to known diseases associated with the pre-selected set of known mutations to identify diseases, if any, indicated by the biological sample. By exploiting a resonant interaction, mutation signatures may be robustly identified even in circumstances involving low signal to noise ratios or, in some cases, negative signal to noise ratios.

31 Claims, 4 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 6

L3: Entry 44 of 53 File: USPT Nov 7, 2000

DOCUMENT-IDENTIFIER: US 6142681 A
TITLE: Method and apparatus for interpreting hybridized bioelectronic DNA microarray patterns using self-scaling convergent reverberant dynamics

Abstract Text (1):
A technique is described for identifying mutations, if any, present in a biological sample, from a pre-selected set of known mutations. The method can be applied to DNA, RNA and peptide nucleic acid (PNA) microarrays. The method analyzes a dot spectrogram representative of quantized hybridization activity of oligonucleotides in the sample to identify the mutations. In accordance with the method, a resonance pattern is generated which is representative of nonlinear resonances between a stimulus pattern associated with the set of known mutations and the dot spectrogram. The resonance pattern is interpreted to a yield a set of confirmed mutations by comparing resonances found therein with predetermined resonances expected for the selected set of mutations. In a particular example, the resonance pattern is generated by iteratively processing the dot spectrogram by performing a convergent reverberation to yield a resonance pattern representative of resonances between a predetermined set of selected Quantum Expressor Functions and the dot spectrogram until a predetermined degree of convergence is achieved between the resonances found in the resonance pattern and resonances expected for the set of mutations. The resonance pattern is analyzed to a yield a set of confirmed mutations by mapping the confirmed mutations to known diseases associated with the pre-selected set of known mutations to identify diseases, if any, indicated by the biological sample. By exploiting a resonant interaction, mutation signatures may be robustly identified even in circumstances involving low signal to noise ratios or, in some cases, negative signal to noise ratios.

Brief Summary Text (12):
Accordingly, it would highly desirable to provide an improved method and apparatus for analyzing the output of the DNA microarray to more expediently, reliably, and inexpensively determine the presence of any conditions within the patient providing the DNA sample. It is particularly desirable to provide a technique that can

identify mutation signatures within dot spectrograms even in circumstance wherein the signal to noise ration is extremely low. It is to these ends that aspects of the invention are generally drawn.

☐ 45. Document ID: US 6136541 A

L3: Entry 45 of 53 File: USPT Oct 24, 2000

US-PAT-NO: 6136541
DOCUMENT-IDENTIFIER: US 6136541 A

TITLE: Method and apparatus for analyzing hybridized biochip patterns using resonance interactions employing quantum expressor functions

DATE-ISSUED: October 24, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gulati; Sandeep	La Canada	CA		

US-CL-CURRENT: 435/6; 382/129, 536/24.3, 536/24.31, 536/24.32, 702/19, 702/20

ABSTRACT:

A technique is described for identifying mutations, if any, present in a biological sample, from a pre-selected set of known mutations. The method can be applied to DNA, RNA and peptide nucleic acid (PNA) microarrays. The method analyzes a dot spectrogram representative of quantized hybridization activity of oligonucleotides in the sample to identify the mutations. In accordance with the method, a resonance pattern is generated which is representative of nonlinear resonances between a stimulus pattern associated with the set of known mutations and the dot spectrogram. The resonance pattern is interpreted to a yield a set of confirmed mutations by comparing resonances found therein with predetermined resonances expected for the selected set of mutations. In a particular example, the resonance pattern is generated by iteratively processing the dot spectrogram by performing a convergent reverberation to yield a resonance pattern representative of resonances between a predetermined set of selected Quantum Expressor Functions and the dot spectrogram until a predetermined degree of convergence is achieved between the resonances found in the resonance pattern and resonances expected for the set of mutations. The resonance pattern is analyzed to a yield a set of confirmed mutations by mapping the confirmed mutations to known diseases associated with the pre-selected set of known mutations to identify diseases, if any, indicated by the biological sample. By exploiting a resonant interaction, mutation signatures may be robustly identified even in circumstances involving low signal to noise ratios or, in some cases, negative signal to noise ratios.

31 Claims, 7 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 6

L3: Entry 45 of 53 File: USPT Oct 24, 2000

DOCUMENT-IDENTIFIER: US 6136541 A
TITLE: Method and apparatus for analyzing hybridized biochip patterns using resonance interactions employing quantum expressor functions

Abstract Text (1):
A technique is described for identifying mutations, if any, present in a biological sample, from a pre-selected set of known mutations. The method can be applied to DNA, RNA and peptide nucleic acid (PNA) microarrays. The method analyzes a dot spectrogram representative of quantized hybridization activity of oligonucleotides in the sample to identify the mutations. In accordance with the method, a resonance pattern is generated which is representative of nonlinear resonances between a stimulus pattern associated with the set of known mutations and the dot spectrogram. The resonance pattern is interpreted to a yield a set of confirmed mutations by comparing resonances found therein with predetermined resonances expected for the selected set of mutations. In a particular example, the resonance pattern is generated by iteratively processing the dot spectrogram by performing a convergent reverberation to yield a resonance pattern representative of resonances between a predetermined set of selected Quantum Expressor Functions and the dot spectrogram until a predetermined degree of convergence is achieved between the resonances found in the resonance pattern and resonances expected for the set of mutations. The resonance pattern is analyzed to a yield a set of confirmed mutations by mapping the confirmed mutations to known diseases associated with the pre-selected set of known mutations to identify diseases, if any, indicated by the biological sample. By exploiting a resonant interaction, mutation signatures may be robustly identified even in circumstances involving low signal to noise ratios or, in some cases, negative signal to noise ratios.

Brief Summary Text (10):
Accordingly, it would highly desirable to provide an improved method and apparatus for analyzing the output of the DNA microarray to more expediently, reliably, and inexpensively determine the presence of any medical conditions or concerns within the patient providing the DNA sample. It is particularly desirable to provide a technique that can identify mutation signatures within dot spectrograms even in circumstance wherein the signal to noise ration is extremely low. It is to these ends that aspects of the invention are generally drawn.

☐ 46. Document ID: WO 3106710 A1

L3: Entry 46 of 53 File: EPAB Dec 24, 2003

PUB-NO: WO003106710A1
DOCUMENT-IDENTIFIER: WO 3106710 A1
TITLE: CORRECTION METHOD, APPARATUS AND RECORDING MEDIUM ON OLIGONUCLEOTIDE MICROARRAY USING PRINCIPAL COMPONENT ANALYSIS

PUBN-DATE: December 24, 2003

INVENTOR-INFORMATION:

NAME	COUNTRY
YOON, YEOIN	KR
PARK, JIN HYUN	KR

INT-CL (IPC): C12 Q 1/68

ABSTRACT:

The present invention relates to correction method, apparatus and recording medium on an oligonucleotide microarray using Principal Component Analysis (PCA). More particularly, the present invention relates to correction method, apparatus and recording medium on the oligonucleotide microarray using the correlation of probe set for detecting and correcting the faulty probe expression data in the outliers of the oligonucleotide microarray by applying PCA to each probe set of gene. Since the faulty probe data is corrected close to the normal value, the present invention makes it possible to remove the noise included in the oligonucleotide microarray, improve the accuracy and efficiency of chip experiment and analysis due to obtainment of accurate expression intensity data, and standardize the oligonucleotide chip data.

L3: Entry 46 of 53 File: EPAB Dec 24, 2003

DOCUMENT-IDENTIFIER: WO 3106710 A1
TITLE: CORRECTION METHOD, APPARATUS AND RECORDING MEDIUM ON OLIGONUCLEOTIDE MICROARRAY USING PRINCIPAL COMPONENT ANALYSIS

Abstract Text (1):
The present invention relates to correction method, apparatus and recording medium on an oligonucleotide microarray using Principal Component Analysis (PCA). More particularly, the present invention relates to correction method, apparatus and recording medium on the oligonucleotide microarray using the correlation of probe set for detecting and correcting the faulty probe expression data in the outliers of the oligonucleotide microarray by applying PCA to each probe set of gene. Since the faulty probe data is corrected close to the normal value, the present invention makes it possible to remove the noise included in the oligonucleotide microarray, improve the accuracy and efficiency of chip experiment and analysis due to obtainment of accurate expression intensity data, and standardize the oligonucleotide chip data.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 47. Document ID: WO 3035911 A1

L3: Entry 47 of 53 File: EPAB May 1, 2003

PUB-NO: WO003035911A1
DOCUMENT-IDENTIFIER: WO 3035911 A1
TITLE: CLONE IDENTIFICATION BY DIRECT DETECTION OF NUCLEIC ACID BINDING PROTEINS FROM VERTEBRATE CELL EXPRESSION SYSTEMS AND APPLICATIONS THEREOF

PUBN-DATE: May 1, 2003

INVENTOR-INFORMATION:

NAME	COUNTRY
DOBI, ALBERT L	US

INT-CL (IPC): C12 Q 1/68; C12 P 19/34; C07 H 21/02; C07 H 21/04; C07 H 19/00
EUR-CL (EPC): C12N015/10

ABSTRACT:

CHG DATE=20030603 STATUS=O>A general vertebrate cloning and screening process for identification of genes encoding nucleic acid binding proteins is disclosed, including steps of library division and protein expression, followed by a nucleic acid binding assay as a clone screening step that is analyzed by either an Electrophoretic Mobility Shift Assay (EMSA) or a chromatography assay, preferably in a high throughput assay format. The disclosed technology provides a complete clone selection system for genes of DNA and RNA binding proteins expressed in vertebrate cells. Included are ways to optimize vertebrate cell transformation or transfection conditions by measuring the nucleic acid binding function of an expressed control protein. Also included is a high throughput electrophoretic mobility shift assay (EMSA) for detection of nucleic acid binding proteins, using a novel application of thin layer agarose gels for EMSA, combining a high vacuum and high temperature blotting technique for agarose gel desiccation with the use of a high efficiency transfer matrix (for instance, quaternary aminated nylon membranes) for blotting nucleic acid-protein complexes from agarose gels. Compensation for sample-to-sample variations in signal-to-noise ratio in clone screening is provided by introducing a reference probe to detect binding of a known protein expressed in the vertebrate host cell, along with the tester probe with the target sequence for which new clones encoding binding proteins are sought. High throughput chromatography screening methodology for nucleic acid binding proteins is also disclosed, allowing automation of screening. The disclosed technology includes combinatorial applications providing assays for functional gene linkage groups and can also be applied in connection with cDNA microarray and protein chip technologies.

L3: Entry 47 of 53 File: EPAB May 1, 2003

DOCUMENT-IDENTIFIER: WO 3035911 A1
TITLE: CLONE IDENTIFICATION BY DIRECT DETECTION OF NUCLEIC ACID BINDING PROTEINS FROM VERTEBRATE CELL EXPRESSION SYSTEMS AND APPLICATIONS THEREOF

Abstract Text (1):
CHG DATE=20030603 STATUS=O>A general vertebrate cloning and screening process for identification of genes encoding nucleic acid binding proteins is disclosed, including steps of library division and protein expression, followed by a nucleic acid binding assay as a clone screening step that is analyzed by either an Electrophoretic Mobility Shift Assay (EMSA) or a chromatography assay, preferably in a high throughput assay format. The disclosed technology provides a complete clone selection system for genes of DNA and RNA binding proteins expressed in vertebrate cells. Included are ways to optimize vertebrate cell transformation or transfection conditions by measuring the nucleic acid binding function of an expressed control protein. Also included is a high throughput electrophoretic mobility shift assay (EMSA) for detection of nucleic acid binding proteins, using a novel application of thin layer agarose gels for EMSA, combining a high vacuum and high temperature blotting technique for agarose gel desiccation with the use of a high efficiency transfer matrix (for instance, quaternary aminated nylon membranes) for blotting nucleic acid-protein complexes from agarose gels. Compensation for sample-to-sample variations in signal-to-noise ratio in clone screening is provided by introducing a reference probe to detect binding of a known protein expressed in the vertebrate host cell, along with the tester probe with the target sequence for which new clones encoding binding proteins are sought. High throughput chromatography screening methodology for nucleic acid binding proteins is also

disclosed, allowing automation of screening. The disclosed technology includes combinatorial applications providing assays for functional gene linkage groups and can also be applied in connection with cDNA microarray and protein chip technologies.

☐ 48. Document ID: WO 3030620 A2

L3: Entry 48 of 53 File: EPAB Apr 17, 2003

PUB-NO: WO003030620A2
DOCUMENT-IDENTIFIER: WO 3030620 A2
TITLE: IMAGING MICROARRAYS

PUBN-DATE: April 17, 2003

INVENTOR-INFORMATION:

NAME	COUNTRY
PIPER, JAMES R	GB

ABSTRACT:

A method of obtaining a corrected image of a microarray includes acquiring an image of a microarray including a target spot, and processing the image to correct for background noise and chip misalignment. The method also includes analyzing the image to identify a target patch, edit debris, and correct for ratio bias; and detecting single copy number variation in the target spot using an objective statistical analysis that includes a t-value statistical analysis. The method provides statistically robust computational processes for accurately detecting genomic variation at the single copy level.

L3: Entry 48 of 53 File: EPAB Apr 17, 2003

DOCUMENT-IDENTIFIER: WO 3030620 A2
TITLE: IMAGING MICROARRAYS

Abstract Text (1):
A method of obtaining a corrected image of a microarray includes acquiring an image of a microarray including a target spot, and processing the image to correct for background noise and chip misalignment. The method also includes analyzing the image to identify a target patch, edit debris, and correct for ratio bias; and detecting single copy number variation in the target spot using an objective statistical analysis that includes a t-value statistical analysis. The method provides statistically robust computational processes for accurately detecting genomic variation at the single copy level.

☐ 49. Document ID: WO 2091211 A1

L3: Entry 49 of 53 File: EPAB Nov 14, 2002

PUB-NO: WO002091211A1
DOCUMENT-IDENTIFIER: WO 2091211 A1
TITLE: KERNELS AND METHODS FOR SELECTING KERNELS FOR USE IN LEARNING MACHINES

PUBN-DATE: November 14, 2002

INVENTOR-INFORMATION:

NAME	COUNTRY
BARTLETT, PETER	US
ELLISSEEFF, ANDRE	US
SCHOELKOPF, BERNARD	DE

INT-CL (IPC): G06 F 15/18

ABSTRACT:

CHG DATE=20030114 STATUS=N>Kernels (206) for use in learning machines, such as support vector machines, and methods are provided for selection and construction of such kernels are controlled by the nature of the data to be analyzed (203). In particular, data which may possess characteristics such as structure, for example DNA sequences, documents; graphs, signals, such as ECG signals and microarray expression profiles; spectra; images; spatio-temporal data; and relational data, and which may possess invariances or noise components that can interfere with the ability to accurately extract the desired information. Where structured datasets are analyzed, locational kernels are defined to provide measures of similarity among data points (210). The locational kernels are then combined to generate the decision function, or kernel. Where invariance transformations or noise is present, tangent vectors are defined to identify relationships between the invariance or noise and the data points (222). A covariance matrix is formed using the tangent vectors, then used in generation of the kernel.

L3: Entry 49 of 53 File: EPAB Nov 14, 2002

DOCUMENT-IDENTIFIER: WO 2091211 A1
TITLE: KERNELS AND METHODS FOR SELECTING KERNELS FOR USE IN LEARNING MACHINES

Abstract Text (1):
CHG DATE=20030114 STATUS=N>Kernels (206) for use in learning machines, such as support vector machines, and methods are provided for selection and construction of such kernels are controlled by the nature of the data to be analyzed (203). In particular, data which may possess characteristics such as structure, for example DNA sequences, documents; graphs, signals, such as ECG signals and microarray expression profiles; spectra; images; spatio-temporal data; and relational data, and which may possess invariances or noise components that can interfere with the ability to accurately extract the desired information. Where structured datasets are analyzed, locational kernels are defined to provide measures of similarity among data points (210). The locational kernels are then combined to generate the decision function, or kernel. Where invariance transformations or noise is present, tangent vectors are defined to identify relationships between the invariance or noise and the data points (222). A covariance matrix is formed using the tangent vectors, then used in generation of the kernel.

☐ 50. Document ID: WO 2003106710 A1

L3: Entry 50 of 53 File: DWPI Dec 24, 2003

DERWENT-ACC-NO: 2004-082209
DERWENT-WEEK: 200408

TITLE: Correcting outlier on oligonucleotide microarray by principal component analysis, by making correlation structure model denoting correlation structure of probes, correcting faulty probe data by projecting model to outlier

INVENTOR: PARK, J H; YOON, Y

PRIORITY-DATA: 2003KR-0038205 (June 13, 2003), 2002KR-0033864 (June 18, 2002)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 2003106710 A1	December 24, 2003	E	052	C12Q001/68

INT-CL (IPC): C12 Q 1/68

ABSTRACTED-PUB-NO: WO2003106710A

BASIC-ABSTRACT:

NOVELTY - Correcting outliers on an oligonucleotide microarray using principal component analysis (PCA), involves constructing a correlation structure model indicating a correlation structure between probes of the oligonucleotide microarray data by use of the PCA, and correcting a faulty probe data by projecting the correlation structure model to the outlier.

DETAILED DESCRIPTION - Correcting (M1) outliers on an oligonucleotide microarray using principal component analysis (PCA), involves constructing a correlation structure model indicating a correlation structure between probes of the oligonucleotide microarray data by use of the PCA or detecting an outlier in the oligonucleotide microarray data, constructing a first correlation structure model for model data to be used to correct the outlier by use of PCA, and correcting a faulty probe data by projecting the correlation structure model to the outlier.

INDEPENDENT CLAIMS are also included for the following:

(1) a computer-readable medium including a program containing computer-executable instructions to perform (M1);

(2) a correction apparatus (I) of an oligonucleotide microarray, comprising a correlation structure model generator for constructing a correlation structure model indicating a correlation structure between probes of the oligonucleotide microarray data by use of the PCA or an outlier extractor for detecting outlier from the oligonucleotide microarray data, a first correlation structure model generator for constructing a first correlation structure model for model data to be used to correct the outlier by use of the PCA, and a data corrector for correcting a faulty probe data by projecting the first correlation structure model to the

outlier; and

(3) a program being executed in a digital processing device controls operations of the digital processing device to perform (M1).

USE - (M1) is useful for detecting and correcting the faulty probe expression data in the outliers of the oligonucleotide microarray by applying PCA to each probe set of gene (claimed). (M1) is useful for preserving the biological characteristics of the raw data.

ADVANTAGE - (M1) efficiently detects and corrects the faulty probe expression data in the outliers of the oligonucleotide microarray by applying PCA to each probe set of gene and effectively removes the noise included in the oligonucleotide microarray. (M1) improves the accuracy and efficiency of chip experiment and analysis due to obtainment of accurate expression intensity data, and standardize the oligonucleotide chip data.

DESCRIPTION OF DRAWING(S) - The figure shows a flowchart of correcting outliers on the nucleotide microarray using principal component analysis (PCA).

L3: Entry 50 of 53 File: DWPI Dec 24, 2003

DERWENT-ACC-NO: 2004-082209
DERWENT-WEEK: 200408

TITLE: Correcting outlier on oligonucleotide microarray by principal component analysis, by making correlation structure model denoting correlation structure of probes, correcting faulty probe data by projecting model to outlier

Basic Abstract Text (8):
ADVANTAGE - (M1) efficiently detects and corrects the faulty probe expression data in the outliers of the oligonucleotide microarray by applying PCA to each probe set of gene and effectively removes the noise included in the oligonucleotide microarray. (M1) improves the accuracy and efficiency of chip experiment and analysis due to obtainment of accurate expression intensity data, and standardize the oligonucleotide chip data.

Term	Documents
IDENTIF$	0
IDENTIF	128
IDENTIFABILITY	1
IDENTIFABLE	26
IDENTIFABLY	2
IDENTIFACATION	8
IDENTIFACTION	21
IDENTIFACTOR	1

IDENTIFACTORY	1
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